BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 579 263 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
16.09.1998 Bulletin 1998/38

(21) Application number: **93113146.0**

(22) Date of filing: **22.06.1988**

(51) Int. Cl.[6]: **C07D 207/09**, C07D 211/26, C07D 211/32, C07D 211/34, C07D 401/06, C07D 405/06, C07D 471/06, C07D 401/12, C07D 405/12

(54) 1,4-Substituted piperidines as acetylchozinesterase inhibitors and their use for the treatment of Alzheimer's disease

1,4-Substituierte Piperidine als Acetylcholinesterase Inhibitoren und ihre Verwendung zur Behandlung von Alzheimer's Erkrankung

Pipéridines 1,4-substituées comme inhibiteurs de l'acétylcholinestérase et leur utilisation dans le traitement de la maladie d'alzheimer

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(30) Priority: **22.06.1987 JP 155058/87**

(43) Date of publication of application:
19.01.1994 Bulletin 1994/03

(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:
88109924.6 / 0 296 560

(73) Proprietor: **Eisai Co., Ltd.**
Tokyo (JP)

(72) Inventors:
- **Sugimoto, Hachiro**
  Ushiku-shi, Ibaraki (JP)
- **Tsuchiya, Yutaka**
  Fort Lee, New Jersey, 07024 (US)
- **Higurashi, Kunizou**
  Sumida-ku, Tokyo (JP)
- **Karibe, Norio**
  Sumida-ku, Tokyo (JP)
- **Iimura, Youichi**
  2-chome, Tsukuba-shi, Ibaraki (JP)
- **Sasaki, Atsushi**
  Tsukuba-shi, Ibaraki (JP)
- **Yamanishi, Yoshiharu**
  Ryugasaki-shi, Ibaraki (JP)
- **Ogura, Hiroo**
  Tsuchiura-shi, Ibaraki (JP)
- **Araki, Shin**
  Tsukuba-shi, Ibaraki (JP)
- **Kosasa, Takashi**
  Tsukuba-shi, Ibaraki (JP)
- **Kusota, Atsuhiko**
  Tsukuba-shi, Ibaraki (JP)
- **Kozasa, Michiko**
  Tsukuba-shi, Ibaraki (JP)
- **Yamatsu, Kiyomi**
  Kamakura-shi, Kanagawa (JP)

(74) Representative:
Hansen, Bernd, Dr. Dipl.-Chem. et al
Hoffmann Eitle,
Patent- und Rechtsanwälte,
Postfach 81 04 20
81904 München (DE)

(56) References cited:

EP-A- 26 749
EP-A- 92 391
EP-A- 112 776
EP-A- 229 391
DE-A- 2 731 299
EP-A- 29 707
EP-A- 111 864
EP-A- 207 913
DE-A- 2 533 567

- **CHEMICAL ABSTRACTS, vol. 101, 1984, Columbus, Ohio, US; abstract no. 151875,**
- **JOURNAL OF ORGANIC CHEMISTRY. vol. 38, no. 17, 1973, EASTON US pages 3004 - 3011 AUGUSTINE ET. AL. 'Synthesis of .alpha.-Monosubstituted Indoles'**
- **Archiv der Pharmazie, vol.307(5), pages 360-66**

Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

EP 0 579 263 B1

Description

The invention relates to a cyclic amine compound, a therapeutical composition and medical treatment of senile dementia.

(Statement of Prior Arts)

With a rapid increase in the population of aged people, the establishment of the therapy for senile dementia, such as Alzheimer senile dementia, is eagerly desired.

Various attempts have been made to treat the senile dementia with a drug. So far, however, there has been no drug which is very useful for the treatment of these diseases.

Studies on the development of therapeutic agents for these diseases have been made from various aspects. Particularly, since Alzheimer senile dementia is accompanied by the lowering in cholinergic hypofunction, the development of the therapeutic agent from the aspect of an acetylcholine precursor and an acetylcholinesterase inhibitor was proposed and is in fact attempted. Representative examples of the anti-cholinesterase inhibitor include physostigmine and tetrahydroaminoacridine. However, these drugs have drawbacks such as an unsatisfactory effect and the occurrence of unfavorable side effects. At the present time, there are no decisive therapeutic agents.

EP-A-0 229 391, having respective priority and filing dates of 27 December 1985 and 24 December 1986, discloses various piperidine derivatives which are useful for preventing dementia.

In view of the above situation, the present inventors have made extensive and intensive studies on various compounds for many years with a view to developing a drug which has a persistent activity and a high safety.

As a result, the present Inventors have found that a piperidine derivative represented by the following general formula (XXV) can attain the desired object.

Specifically, the compound of the present invention represented by the following general formula (XXV) has great advantages of having strong and highly selective antiacetylcholinesterase activity, increasing the amount of acetylcholine present in the brain, exhibiting an excellent effect on a model with respect to disturbance of memory, and having a persistent activity and a high safety when compared with physostigmine which is a conventional popular drug in the art, which renders the compound of the present invention very valuable.

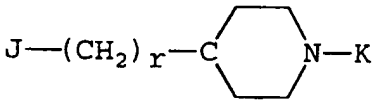
The compound of the present invention was found based on the acetylcholinesterase inhibitory action and, therefore, is effective for treatment and prevention of various diseases which are thought to be derived from the deficiency of acetylcholine as a neurotransmitter in vivo.

Examples of such diseases include various kinds of dementia including Alzheimer senile dementia and further include Huntington's chorea, Pick's disease, and ataxia.

Therefore, the objects of the present invention are to provide a novel piperidine derivative effective as a pharmaceutical, particularly for treatment and prevention of central nervous system diseases, and to provide a pharmaceutical comprising the same as an effective ingredient.

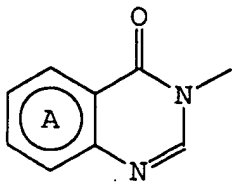
(Summary of the Invention)

The invention provides a cyclic amine compound having the following formula (XXV) and a pharmacologically acceptable salt thereof:

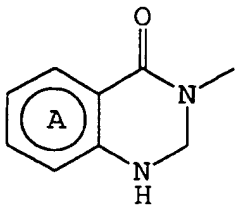


(XXV)

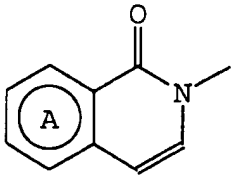
wherein J is a monovalent group selected from



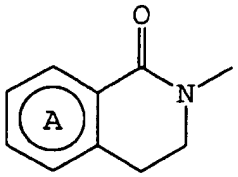
(a)



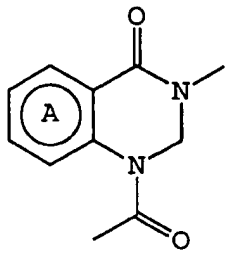
(b)



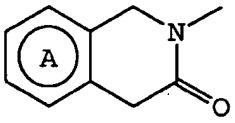
(c)



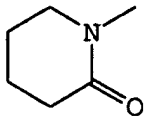
(d)



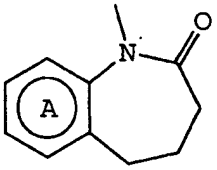
(e)



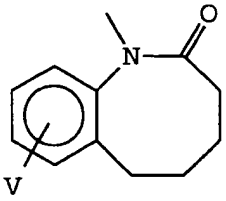
(g)



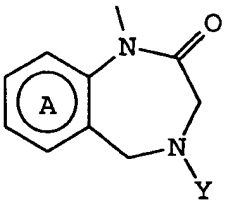
(h)



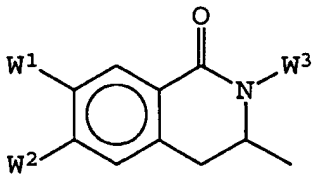
(j)



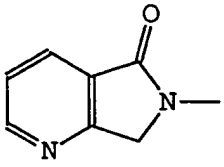
(k)



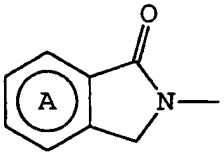
(l)



(n)



(p)



(q)

wherein

Y in the formula (l) is a hydrogen atom or a C_{1-6} alkyl group; V in the formula (k) is a hydrogen atom or a C_{1-6} alkoxy group; W^1 and W^2 in the formula (n) are each a hydrogen atom, a C_{1-6} alkyl or a C_{1-6} alkoxy group; W^3 in formula

(n) is a hydrogen atom or a C_{1-6} alkyl group; and the phenyl group A in the formulae (a)-(g), (j), (l) and (q) may optionally be substituted by a C_{1-6} alkyl group or a C_{1-6} alkoxy group;

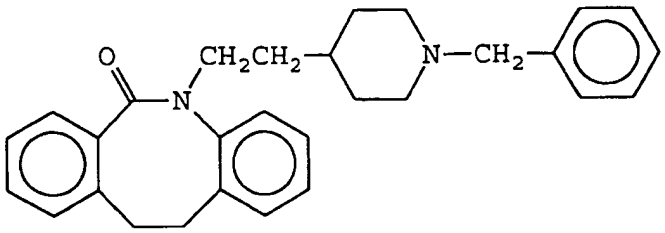
K is a phenylalkyl group wherein the phenyl may optionally be substituted by a C_{1-6} alkyl group which may optionally be halogenated, a C_{1-6} alkoxy group, a nitro group, a halogen atom, a carboxyl group, a benzyloxy group, a C_{1-6} alkoxycarbonyl group, an amino group, a C_{1-6} monoalkylamino group, a C_{1-6} dialkylamino group, a carbamoyl group, a C_{1-6} acylamino group, a cyclohexyloxycarbonyl group, a C_{1-6} alkylaminocarbonyl group, a C_{1-6} alkylcarbonyloxy group, a hydroxyl group, a formyl group or a C_{1-6} alkoxy-C_{1-6} alkyl group; and

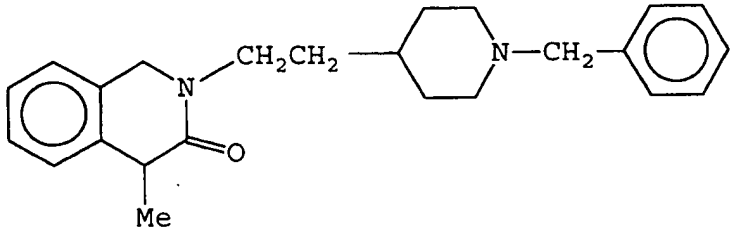
r is an integer of from 0 to 6,

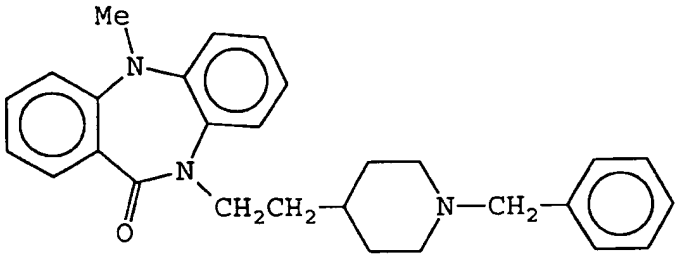
with the proviso that if r is 0, then J is neither the group (a) nor the group (q), and with the proviso that if K is a benzyl group and r is 0, then J is not the group (d).

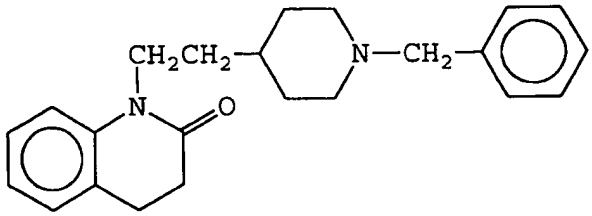
Preferably r is 2.

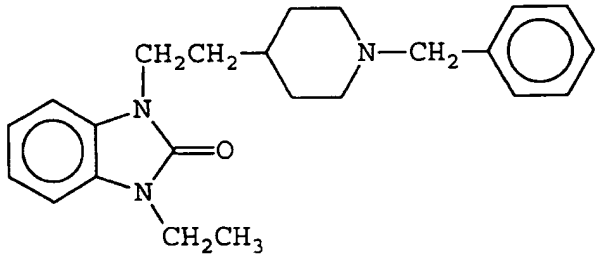
According to a further aspect, the present invention provides a cyclic amine of the formula:

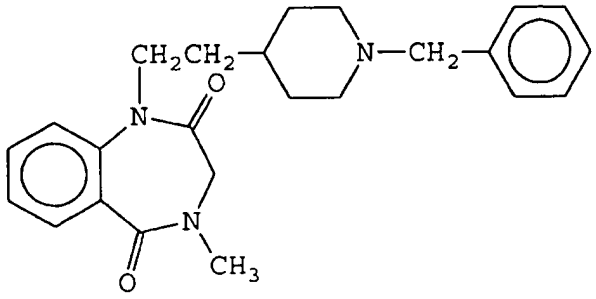




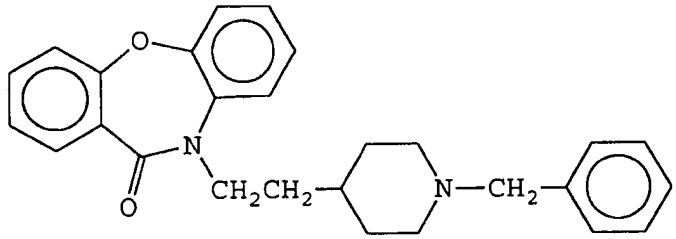








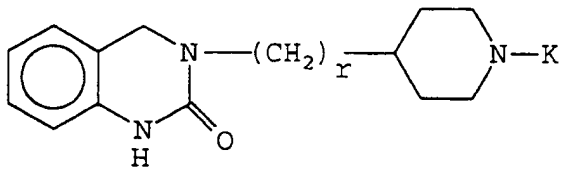
or;



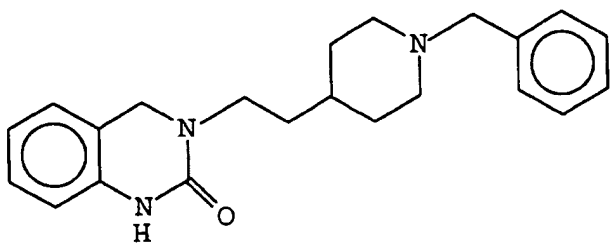
In addition, the invention provides a therapeutical composition which comprises a pharmacologically effective amount of the cyclic amine compound having the formula (XXV) or a pharmacologically acceptable salt thereof and a pharmacologically acceptable carrier.

The use is also provided of any of the above amine compounds, including those excluded by the provisos concerning the index "r" and group "J", for preparing a medicament for the treatment of a disease caused by acetylcholinesterase activity.

In a further aspect, the use is also provided of a cyclic amine compound of the general formula:



wherein the phenyl group of the quinazolinone moiety may optionally be substituted by a C_{1-6} alkyl group or a C_{1-6} alkoxy group, and K and r are as defined in Claim 1 or a pharmacologically acceptable salt thereof, for preparing a medicament for the treatment of a disease caused by acetylcholinesterase activity. Preferably, the cyclic amine compound in this aspect has the formula:



Examples of C_{1-6} alkyl groups present in the above compounds include straight-chain or branched alkyl groups and include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl (amyl), isopenthyl, neopentyl, tert-

pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2 trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl, and 1-ethyl-2-methylpropyl groups. Among them, methyl, ethyl, propyl and isopropyl groups are preferable. A methyl group is the most preferable.

Preferred C_{1-6} alkoxy groups are derived from such alkyl groups.

The phenyl ring "A" in the above formulae (a)-(g), (j), (l) and (q) may be substituted with a lower alkyl group having 1 to 6 carbon atoms, preferably a methyl group, or a lower alkoxy group having 1 to 6 carbon atoms, preferably a methoxy group.

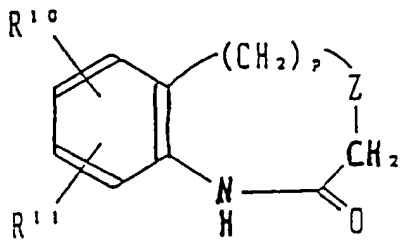
In the present invention, the term "pharmacologically acceptable salt" include those of inorganic acids, such as hydrochloride, sulfate, hydrobromide, and phosphate, and those of organic acids, such as formate, acetate, trifluoroacetate, methanesulfonate, benzenesulfonate, and toluenesulfonate. Further, when a certain kind of substituent is selected, the compound of the present invention may form, e.g., alkali metal salts such as a sodium or potassium salt, alkaline earth metal salts such as a calcium or magnesium salt, organic amine salts such as a salt with trimethylamine, triethylamine, pyridine, picoline, dicyclohexylamine, or N,N'-dibenzylethylenediamine.

Moreover, the compounds of the present invention may have an asymmetric carbon atom depending upon the kind of the substituent and, therefore, have stereoisomers. They are, of course, within the scope of the present invention.

The compound of the present invention may be prepared by various processes. Representative processes for preparing the compound of the present invention will now be described.

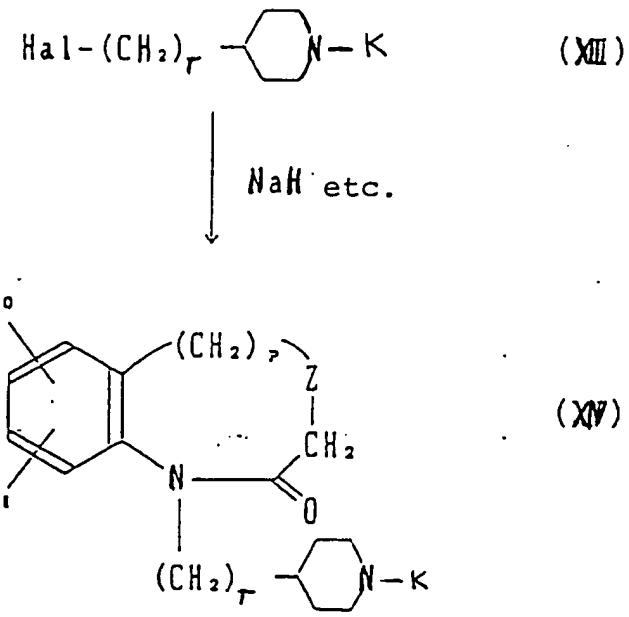
Process A

When J is a monovalent group derived from a cyclic amide compound selected from among the monovalent groups j, k and l, the compound of the present invention can be prepared also by the following process:



(XII)

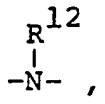
+



(XIII)

(XIV)

wherein R^{10} and R^{11} are each a hydrogen atom, a lower alkyl group, a lower alkoxy group, or a halogen atom, r is an integer of 1 to 6, p is an integer of 1 to 3 and Z is a group represented by the formula $-CH_2-$ or a group represented by the formula

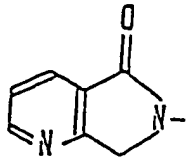


wherein R^{12} is a hydrogen atom or a lower alkyl group.

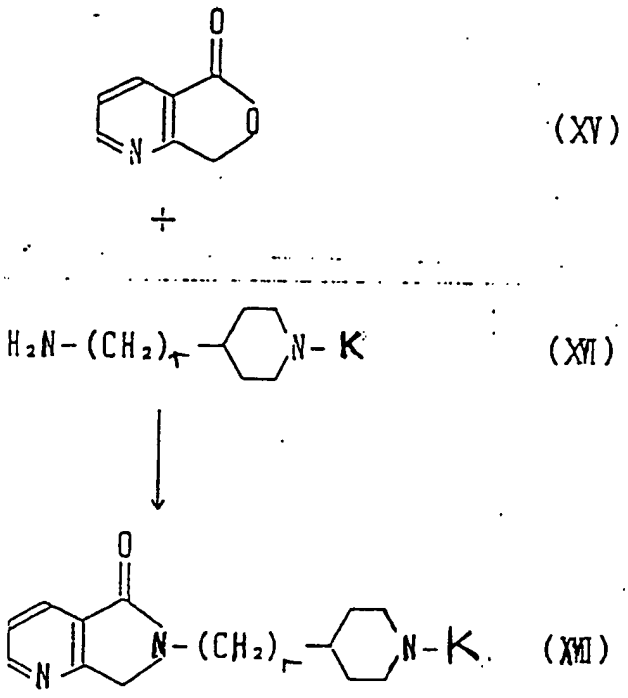
Specifically, a substituted 1,2,3,4-tetrahydro-5H-1-benzazepin-2-one is allowed to condense with a substituted N-benzyl-4-(2-halogenoethyl)piperidine represented by the general formula (XIII) in a solvent, e.g., dimethylformamide, in the presence of, e.g., sodium hydride, thereby preparing a compound (XIV) which is one of the object compounds.

Process B

When J is a group represented by the formula,



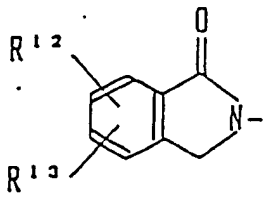
the compound of the present invention can be prepared also by the following process:



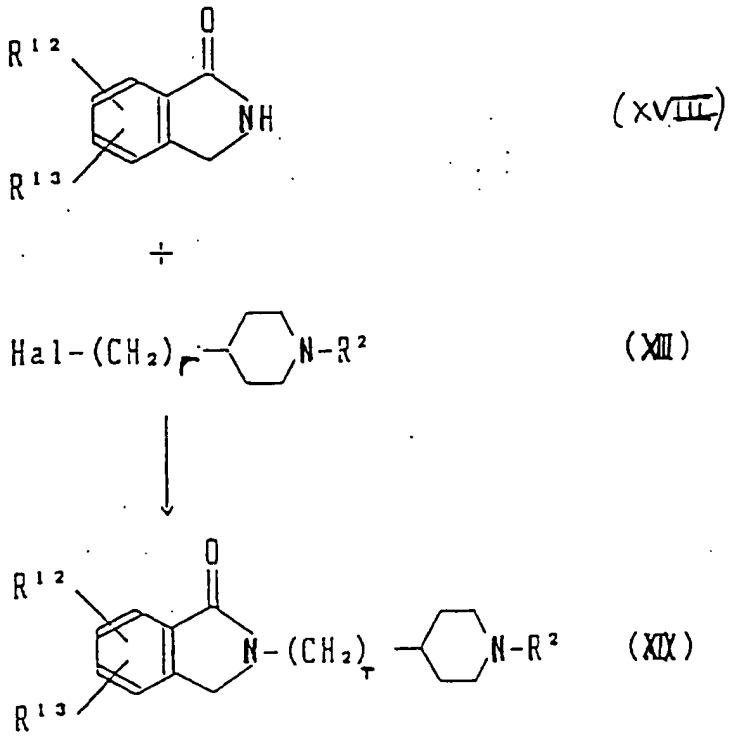
Specifically, 2-hydroxymethylnicotinic acid lactone (XV) is reacted with a substituted N-benzyl(2-aminoethyl)-piperidine represented by the general formula (XVI) by an ordinary method to prepare a compound represented by the general formula (XVII) which is one of the object compounds. The reaction temperature is preferably about 200°C.

Process C

When J in the general formula (I) is a group represented by the formula



, the compound of the present invention can be prepared also by the following process:



Specifically, a substituted 2,3-dihydroxypyrrolo(3,4-b)benzene represented by the general formula (XVIII) is reacted with a substituted N-benzyl(2-halogenoethyl)piperidine represented by the general formula (XIII) in the presence of, e.g., sodium hydride, in a solvent, such as dimethylformamide, while heating the reaction mirture, thereby preparing a compound (XIX) which is one of the object compounds.

The compounds thus prepared and acid addition salts thereof represented by the general formula (I) are useful for treatment of various kinds of senile dementia, in particular senile dementia of the Alzheimer type.

The invention will be described in view of its therapeutical usefulness together with pharmacologically experimental data.

Experimental Example 1

In vitro acetylcholinesterase inhibitory action

A mouse brain homogenate was used as an acetylcholinesterase source and the esterase activity thereof was determined according to the method of Ellman et al.

Ellman, G.L., Courtney, K.D., Andres, V., and Featherstone, R.M., (1961) Biochem. Pharmacol., 7, 88-95.

Acetylthiocholine as a substrate, a sample to detect and DTNB were added to the mouse brain homogenate, followed by incubation. The amount of a yellow substance formed by the reaction between the thiocholine and DTNB was determined in the absorbance at 412 nm in terms of the acetylcholinesterase activity.

The acetylcholinesterase inhibitory activity of the sample was expressed in terms of inhibitory concentration 50% (IC_{50}).

The results are shown in Table 1.

Table 1

Compound	AChE inhibitory activity IC_{50} (μM)	Compound	AChE inhibitory activity IC_{50} (μM)
5	0.10		
6	0.017		

Table 1 (continued)

Compound	AChE inhibitory activity IC_{50} (μM)	Compound	AChE inhibitory activity IC_{50} (μM)
8	0.013	52	0.80
9	0.051	54	1.0
10	0.009	56	0.017
11	0.063	62	0.0075
12	0.040	65	0.0016
		67	0.10
		70	0.28
		176	0.004

Experimental Example 3

Action on passive avoidance learning impairment induced by scopolamine

See Z.Bokolanecky & Jarvik:Int.J.Neuropharmacol, 6, 217-222(1967).

Male Wister rats were used as the test animal and a step-through light and dark box was used as an apparatus. A sample to detect was orally administered one hour before the training and the rats were treated with 0.5 mg/kg (i.p.) of scopolamine 30 min. before the training. In a training experiment, the animal was placed into a light room and, just after the animal had entered into a dark room, a guillotine door was closed, followed by delivery of an electric shock from the gid of the floor. After six hours, the animal was again placed into a light room for a retention experiment, and the time taken for the animal to enter the dark room was measured for evaluation of the effect of the sample.

The difference in the response time between the physiological saline administration group and the scopolamine administration group was taken as 100%, and the effect of the sample was expressed in terms of the percentage antagonism by the sample (Reverse %).

The results are shown in Table 3.

Table 3

Compd. No.	Dose (mg/kg)	Reverse %
69	0.5	22
	1.0	38

The number of animals per dose was 10 to 17.

NE: non-effective

The above-described pharmacological experiments revealed that the compound of the present invention had a potent acetylcholinesterase inhibitory action.

Therefore, the objects of the present invention are to provide a novel compound effective for various kinds of dementia and the sequelae of cerebrovascular diseases, to provide a process for preparing the same, and to provide a novel pharmaceutical comprising the same as an effective ingredient.

A representative compound of the present invention (Compd. No. 69 in the above Table 3) was applied to toxicity tests on rats. As a result, all the compounds exhibited a toxicity of 100 mg/kg or more, i.e., exhibited no serious toxicity.

The compound of the present invention is effective for treatment, prevention, remission, improvement, etc. of various kinds of senile dementia, particularly senile dementia of the Alzheimer type; cerebrovascular diseases accompanying cerebral apoplexy, e.g. cerebral hemorrhage or cerebral infarcts, cerebral arteriosclerosis, head injury, etc.; and aprosexia, disturbance of speech, hypobulia, emotional changes, recent memory disturbance, hallucinatory-paranoid syndrome, behavioral changes, etc. accompanying encephalitis, cerebral palsy, etc.

Further, the compound of the present invention has a strong and highly selective anticholinesterase action, which renders the compound of the present invention useful also as a pharmaceutical based on this kind of action.

Specifically, the compound of the present invention is effective for, for example, Huntington's chorea, Pick's disease

and delayed ataxia or tardive dyskiaesia other than senile dementia of the Alzheimer type.

When the compound of the present invention is used as a pharmaceutical for these diseases, it may be orally or parenterally administered. In general, it is parenterally administered in the form of injections, such as intravenous, subcutaneous, and intramuscular injections, suppositories, or sublingual tablets. The does will remarkably vary depending upon the symptom; age, sex, weight, and sensitivity of patients; method of administration; time and intervals of administration and properties, dispensing, and kind of pharmaceutical preparations; kind of effective ingredients, etc., so that there is no particular limitation with respect to the dose. Normally the compound may be administered in a dose of about 0.1 to 300 mg, preferably 1 to 100 mg, per day per adult, ordinarily in one to four portions.

Pharmaceutical preparations in the dosage form of, e.g., injections, suppositories, sublingual tablets, tablets, and capsules are prepared according to a method which is commonly accepted in the art.

In preparing injections, the effective ingredient is blended, if necessary, with a pH modifier, a buffer, a suspending agent, a solubilizing agent, a stabilizer, a tonicity agent, a preservative, etc., followed by preparation of an intravenous, subcutaneous, or intramuscular injection according to an ordinary method. In this case, if necessary, it is possible to lyophilize these preparations according to an ordinary method.

Examples of the suspending agents include methylcellulose, Polysorbate 80, hydroxyethylcellulose, acacia, powdered tragacanth, sodium carboxymethylcellulose, and polyoxyethylene sorbitan monolaurate.

Examples of the solubilizing agent include polyoxyethylene hydrogenated castor oil, Polysorbate 80, nicotinamide, polyoxyethylene sorbitan monolaurate, Macrogol, and an ethyl ester of castor oil fatty acid.

Examples of the stabilizer include sodium sulfite, sodium metasuifite, and ether, and examples of the preservative include methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate, sorbic acid, phenol, cresol, and chlorocresol.

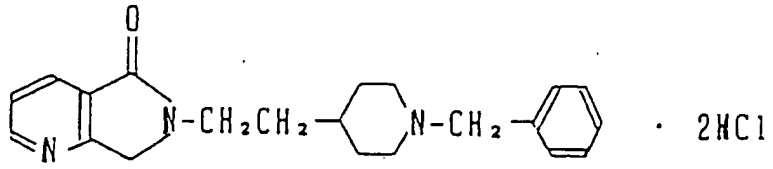
[Examples]

The present invention will now be described in more detail with reference to the following Examples. It is needless to say that the technical scope of the invention of the present invention is not limited to these Examples only.

In the following examples, all of the NMR values are those of the compounds measured in free form.

Example 5

2-[4'-(1'-Benzylpiperidine)ethyl]-2,3-dihydro-1-oxypyrrolo[3,4-b]pyridine dihydrochloride



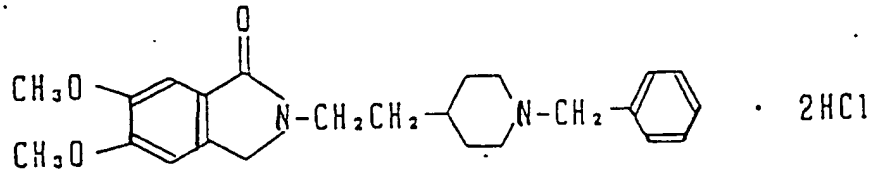
12.6 g of 2-hydroxymethylnicotinic acid lactone and 40 g of 4-(2-aminoethyl)benzylpiperazine were stirred in a sealed tube at 200°C for 7 hr. Thereafter, the reaction mixture was purified by making use of a silica gel column, and a hydrochloride of the purified product was prepared by an ordinary method, thereby preparing 6.37 g of dihydrochloride of the object compound.

- m.p. (°C): 143.5-145°C

• elementary analysis: $C_{21}H_{25}N_3O \cdot 2HCl$			
	C	H	N
calculated (%)	61.77	6.66	10.29
found (%)	61.49	6.68	9.98

Example 6

2-[4'-(1'-Benzylpiperidine)ethyl]-2,3-dihydro-5,6-dimethoxyoxypyrrolo[3,4-b]benzene hydrochloride

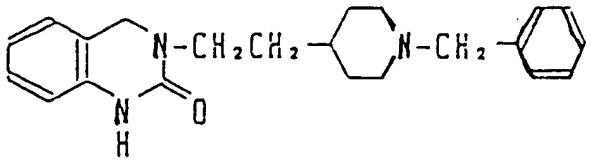


0.5 g of 2,3-dihydro-5,6-dimethoxyoxypyrrolo[3,4-b]benzene was dissolved together with a catalytic amount of potassium iodide in DMF. 0.21 g of sodium hydride (60%) was added to the resulting solution while cooling and stirring the solution. Thereafter, 1 g of 2,3-dihydro-5,6-dimethoxyoxypyrrolo[3,4-b]-benzene was added thereto, and the mixture was stirred at 80°C for 4 hr. After the completion of the stirring, H_2O was added thereto, followed by extraction with chloroform. The chloroform phase was washed with water and dried (over $MgSO_4$). The solvent was distilled off, and the residue was purified with silica gel, thereby preparing an oleaginous object compound. A hydrochloride of the object compound was prepared by an ordinary method, thereby obtaining about 0.2 g of a creamy crystal.

- molecular formula; $C_{24}H_{30}N_2O_3 \cdot 2HCl$
- ^{1}H-NMR($CDCl_3$) δ ;
  1.12~3.4(9H,m), 2.72 ~3.00(2H,m), 3.48(2H,s), 3.62(2H,t), 3.95(6H,s), 4.26(2H,s), 6.90(1H,s), 7.28(6H,s)

Example 8

3-[2-(1-Benzyl-4-piperidyl)ethyl-2-(1H,3H)-quinazolinone



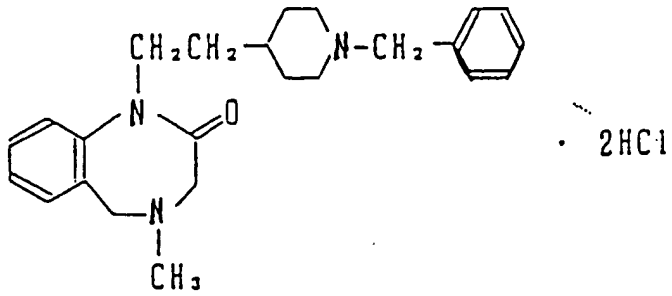
25.6 g of 4-[N-(o-aminobenzyl)ethyl]-1-benzylpiperidine, 15 g of 1,1'-carbonyldiimidazole, and 100 mℓ of methanol were heated under reflux for 12 hr. After the completion of the reaction, the reaction mixture was poured into water, extracted with methylene chloride and dried over magnesium sulfate. The solvent was distilled off in vacuo therefrom.

The residue was purified by silica gel column chromatography (5% MeOH-$CH_2C\ell_2$) and recrystallized twice from ethyl acetate, thereby preparing 3.0 g the title compound.

- molecular formula; $C_{22}H_{27}N_3O$
- ^{1}H-NMR($CDCl_3$) δ ; 1.0 ~2.1(9H,m) 、2.7 ~3.0(2H,m) 、3.2 ~3.6(4H,m) 、4.4 (2H,s) 、6.5 ~7.4(8H,m) 、7.75(1H,s)

Example 9

1-[4'-(1'-Benzylpiperidine)ethyl-1,2,3,4-tetrahydro-4-methyl-5H-[1,4]-benzodiazepin-2-one dihydrochloride

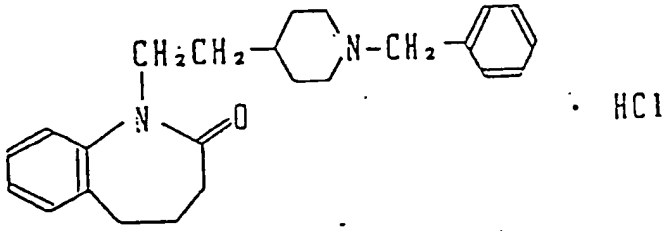


0.35 g of sodium hydride was suspended in 0.5 mℓ of dimethylformamide (DMF). The suspension was stirred while cooling it with ice, and 0.52 g of 1,2,3,4-tetrahydro-4-methyl-5H-[1,4]-benzodiazepin-2-one dissolved in 3 mℓ of DMF was dropwise added thereto, followed by stirring at room temperature for 30 min. 0.81 g of N-benzyl-4-(2-chloromethyl)piperidine hydrochloride dissolved in 3 mℓ of DMF was dropwise added thereto, and the mixture was stirred at 60 to 70°C for 7 hr. The reaction mixture was poured into ice/water and extracted with methylene chloride. The extract was washed with a saturated saline solution and dried over magnesium sulfate. The solvent was distilled off in vacuo. The residue was purified by silica gel column chromatography. A hydrochloride of the purified product was prepared by an ordinary method. Thus there was obtained 0.17 g of a pale yellow amorphous substance (yield: 13.5%).

- molecular formula; $C_{24}H_{31}N_3O \cdot 2HCl$
- ^{1}H-NMR($CDCl_3$) δ ; 1.25~2.02(9H,m)、2.52 (3H,s)、2.79~2.95(2H, bd) 、3.10(2H, s)、3.48(2H,s) 、3.54(2H,s)、3.91(2H, bt) 、7.14~7.45(9H,m)

Example 10

1-[4'-(1'-Benzylpiperidine)ethyl]-1,2,3,4-tetrahydro-5H-1-benzazepin-2-one hydrochloride

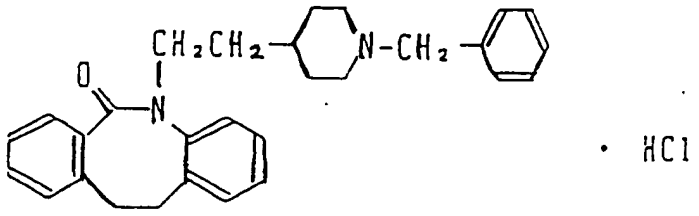


0.27 g of sodium hydride was suspended in 0.5 mℓ of dimethylformamide (DMF). The suspension was stirred while cooling it with ice. 0.60 g of 1,2,3,4-tetrahydro-5H-1-benzazepin-2-one dissolved in 4 mℓ of DMF was dropwise added thereto. The mixture was heated at 60°C for 15 min and then cooled with ice. 1.02 g of N-benzyl-4-(2-chloromethyl)piperidine hydrochloride was added thereto, and the mixture was stirred at 60°C for 3.5 hr. The reaction mixture was left to stand for cooling, poured into ice/water, and extracted with methylene chloride. The extract was washed with water and dried over magnesium sulfate. The solvent was distilled off in vacuo. The residue was purified by silica gel column chromatography. A hydrochloride of the purified product was prepared by an ordinary method. Thus there was obtained 1.40 g of the title compound (yield: 94.8%).

- molecular formula; $C_{24}H_{30}N_2O \cdot HCl$
- ^{1}H-NMR($CDCl_3$) δ ; 1.20~1.92(11H,m) 、2.20 ~2.24(4H, bs) 、2.60~2.88(4H,m)、3.44 (2H,s)、7.12~7.24(9H,m)

Example 11

N-[4-(1'-Benzylpiperidyl)ethyl]-5,6,11,12-tetrahydrodibenzo[b,f]azocin-6-one hydrochloride



· HCl

2.24 g of 5,6,11,12-tetrahydrobenzo[b,f]azocin-6-one and 60% sodium hydride were added to 20 mℓ of dimethylformamide. The mixture was stirred at 60°C for 1 hr, and 0.7 g of 1-benzyl-4-chloroethylpiperidine was added thereto, followed by the reaction for an additional 3.5 hr.

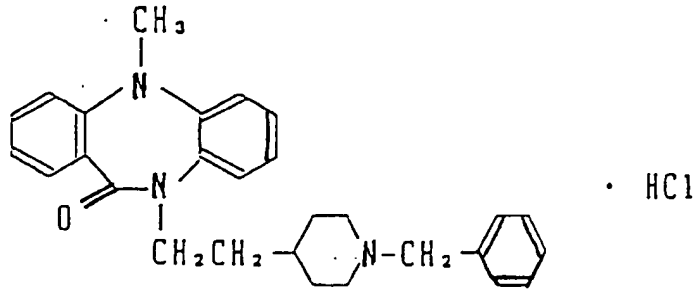
The reaction mixture was poured into 20 mℓ of water, extracted with ethyl acetate, washed with a saturated saline solution, and dried over magnesium sulfate. The solvent was distilled off therefrom in vacuo.

The residue was purified by silica gel column chromatography (5% MeOH in $CH_2C\ell_2$), thereby preparing 0.6 g of the title compound.

- molecular formula; $C_{29}H_{32}N_2O \cdot HCl$
- ^{1}H-NMR($CDCl_3$) δ ; 1.1 ~2.2(9H,m) 、3.7 ~4.1(4H,m) 、4.15~4.5(2H,m) 、4.46 (2H,s)、6.8 ~7.4(13H,m)

Example 12

10-[4'-(1'-Benzylpiperidine)ethyl]-10,11-dihydro-5-methyl-5H-dibenzo[b,e][1,4]diazepin-11-one hydrochloride



· HCl

0.25 g of sodium hydride was suspended in dimethylformamide (DMF). The suspension was stirred while cooling it with ice. 0.58 g of 10,11-dihydro-5-methyl-5H-dibenzo[b,e][1,4]diazepin-11-one dissolved in 5 mℓ of DMF was dropwise added thereto. The mixture was stirred at 40 to 50°C for 20 min and then cooled with ice. 0.71 g of 4-(aminoethyl)-1-benzylpiperidine was added thereto, and the mixture was stirred at 45 to 55°C for 6 hr. The reaction mixture was poured into ice/water and extracted with methylene chloride. The organic phase was washed with a saturated saline solution and dried over magnesium sulfate. The solvent was distilled off in vacuo. The residue was purified by silica gel column chromatography. A hydrochloride of the purified product was prepared by an ordinary method. Thus there was obtained 0.78 g of a pale yellow amorphous substance (yield: 65.4%).

- molecular formula; $C_{28}H_{31}N_3O \cdot HCl$
- ^{1}H-NMR($CDCl_3$) δ ; 1.20~1.91(11H,m) 、2.60~3.00(2H,bs) 、3.22(3H,s) 、3.41 (2H,s) 、6.87~7.08(3H, m)、7.08(9H,m) 、7.64(1H,dd)

Examples 51-56, 58-71 and 176

The compounds synthesized in the same manner as that of Examples 5, 6 and 8-12 are shown in Table 4.

Table 4

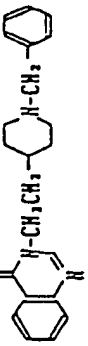
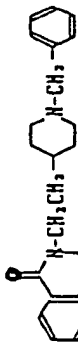
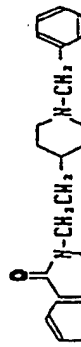
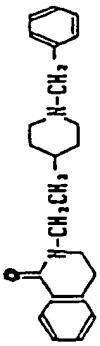
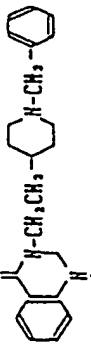
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
51		m.p. (°C); 135~140 (dec.) elem. anal.: $C_{22}H_{25}N_3O \cdot 2HCl$ C H N calcd. (%) 62.86 6.47 10.00 found (%) 59.22 6.63 9.14 $3/2H_2O$ (%) 59.06 6.76 9.39
52		m.p. (°C); 80~82 (dec.) elem. anal.: $C_{22}H_{27}N_3O \cdot 2HCl$ C H N calcd. (%) 62.56 6.92 9.95 found (%) 60.14 7.313 9.21 $1 \cdot H_2O$ (%) 60.00 7.09 9.54
53		^{1}H-NMR($CDCl_3$) δ; 1.1~2.2(9H,m), 2.7~3.1(2H,m), 3.50(2H,s) 4.03(2H,t), 6.50(1H,m), 6.9~7.9(9H,m), 8.47(1H,d) mol. form.; $C_{23}H_{26}N_2O \cdot HCl$
54		^{1}H-NMR($CDCl_3$) δ; 1.1~2.2(9H,m), 2.7~3.1(4H,m), 3.4~3.7 (6H,m), 7.0~7.6(8H,m), 8.06(1H,m) mol. form.; $C_{23}H_{28}N_2O \cdot HCl$
55		^{1}H-NMR($CDCl_3$) δ; 1.10~2.20(11H,m), 2.27(3H,m), 2.93(2H,bd), 3.48~3.70(4H,m), 7.27(5H,s), 7.28~8.12 (4H,m) mol. form.; $C_{24}H_{29}N_3O_2 \cdot HCl$

Table 4 (cont'd)

Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
56	 · HCl	^{1}H-NMR(CDCl$_3$)δ; 1.10~2.20(9H,m) 2.93(2H,bd), 3.40~3.65 (6H,m), 4.43(2H,s), 7.00~7.50(4H,m), 7.31(5H,s) mol. form.; $C_{23}H_{28}N_2O$·HCl
58	 · HCl	^{1}H-NMR(CDCl$_3$)δ; 1.10~2.16(13H,m), 2.16~2.50(2H,m), 2.87 (2H,bd), 3.03~3.43(4H,m), 3.48(2H,s), 7.27(5H,s) mol. form.; $C_{19}H_{20}N_2O$·HCl
59	 · HCl	^{1}H-NMR(CDCl$_3$)δ; 1.10~2.10(9H,m), 1.46(3H,d), 2.87(2H,bd), 3.35~3.72(3H,m), 3.46(2H,s), 4.40(2H,dd), 7.00~7.38(4H,m), 7.28(5H,s) mol. form.; $C_{24}H_{30}N_2O$·HCl
60	· HCl	^{1}H-NMR(CDCl$_3$)δ; 1.20~2.84(2H,m), 3.44(2H,s), 7.14~7.25 (9H,m) mol. form.; $C_{25}H_{32}N_2O$·HCl

Table 4 (cont'd)

Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
61	· HCl	^{1}H-NMR($CDCl_3$)δ; 1.44~1.80(15H,m), 2.96(2H,bs), 2.56(2H,s), 7.08~7.40(9H,m) mol. form.; $C_{23}H_{20}N_2O$·HCl
62	· HCl	^{1}H-NMR($CDCl_3$)δ; 1.24~2.50(5H,m), 2.18(2H,bs), 2.54~2.88 (4H,m), 3.44(2H,s), 3.76(3H,s), 6.64~6.76 (2H,m), 6.99(1H,d), 7.20(5H,s) mol. form.; $C_{25}H_{32}N_2O_2$·HCl
63	· HCl	^{1}H-NMR($CDCl_3$)δ; 1.25~2.20(15H,m), 2.58(2H,bt), 2.86(2H,bs), 3.48(2H,s), 3.75(3H,s), 6.56~6.68(2H,m), 7.00(1H,d), 7.21(5H,s) mol. form.; $C_{25}H_{32}N_2O_2$·HCl
64	· HCl	^{1}H-NMR($CDCl_3$)δ; 1.38~2.02(12H,m), 2.96(2H,d), 5.60(2H,s), 4.94(4H,m), 7.08~7.36(9H,m) mol. form.; $C_{23}H_{29}N_3O$·HCl
65	· HCl	^{1}H-NMR($CDCl_3$)δ; 1.32~2.36(15H,m), 2.84~3.02(2H,m), 3.59(2H,s), 4.09(3H,s), 6.72~6.88(2H,m), 7.20~7.44(7H,m) mol. form.; $C_{25}H_{32}N_2O_2$·HCl

Table 4 (cont'd)

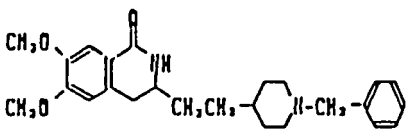
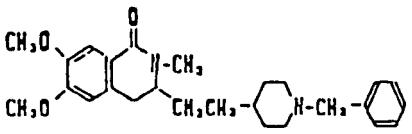
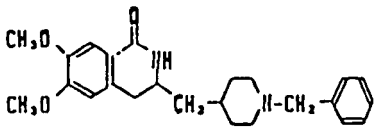
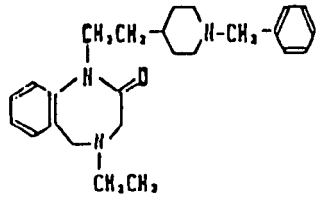
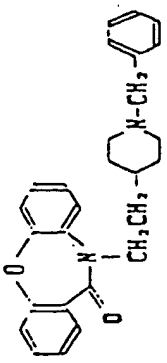
Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
66	 · HCl	^{1}H-NMR($CDCl_3$) δ; 1.10∿2.10(11H,m), 2.60∿3.00(4H,m), 3.45 (2H,s), 3.45∿3.80(1H,m), 3.86(6H,s), 6.22 (1H,bs), 6.57(1H,s), 7.20(5H,s), 7.46(1H,s) mol. form.; $C_{25}H_{32}N_2O_3 \cdot HCl$
67	 · HCl	^{1}H-NMR($CDCl_3$) δ; 1.08∿2.10(11H,m), 2.50∿2.95(4H,m), 3.01 (3H,s), 3.45(2H,s), 3.45∿3.60(1H,m), 3.85 (6H,s), 6.52(1H,s), 7.10(1H,s), 7.20(5H,s) mol. form.; $C_{26}H_{34}N_2O_3 \cdot HCl$
68	 · HCl	^{1}H-NMR($CDCl_3$) δ; 1.02∿2.12(9H,m), 2.50∿3.05(4H,m), 3.43(2H, s), 3.43∿3.85(1H,m), 3.88(6H,s), 6.58(1H, s), 6.50∿6.82(1H,m), 7.20(5H,s), 7.46(1H, s) mol. form.; $C_{24}H_{30}N_2O_3 \cdot HCl$
69	 · 2HCl	^{1}H-NMR($CDCl_3$) δ; 1.17(3H,t), 1.10∿2.15(9H,m), 2.68(2H,q), 2.89(2H,bd), 3.14(2H,s), 3.51(2H,s), 3.55(2H,s), 3.87(2H,bt), 7.07∿7.35(9H,m) mol. form.; $C_{25}H_{33}N_3O \cdot 2HCl$

Table 4

Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
70	 · HCl	^{1}H-NMR($CDCl_3$)δ; (in free form) 1.01~2.40(9H,m), 2.70~3.30(4H,m), 3.46(3H,s), 3.54(2H,s), 3.90~4.20(2H,m), 6.90~8.20(9H,m) mol. form.: $C_{24}H_{29}N_3O_2$·HCl
71	 · HCl	^{1}H-NMR($CDCl_3$)δ; 1.12~2.12(9H,m), 2.76~3.00(2H,m), 3.50(2H,s), 3.66(2H,t), 4.36(2H,s), 7.08~7.92(9H,m)

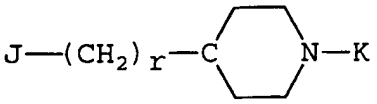
Table 4 (cont'd)

Ex. No.	Structural formula	Physicochemical constant (m.p., elem. anal., NMR, etc.)
176	 · HCl	^{1}H-NMR($CDCl_3$) δ; 9.90∿2.10(9H,m), 2.81(2H,bd), 3.45(2H,s), 4.11(2H,t), 6.98∿7.82(8H,m), 7.21(5H,s) mol. form.; $C_{27}H_{28}N_2O_2 \cdot HCl$

Claims

Claims for the following Contracting States : AT, BE, CH, LI, DE, FR, GB, IT, LU, NL, SE

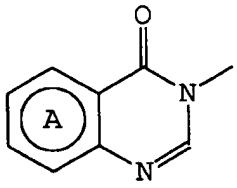
1. A cyclic amine compound having the following formula (XXV) or a pharmacologically acceptable salt thereof:



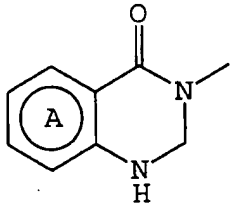
(XXV)

wherein

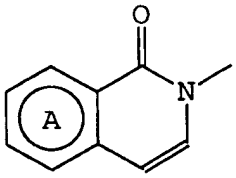
J is a monovalent group selected from



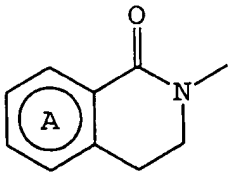
(a)



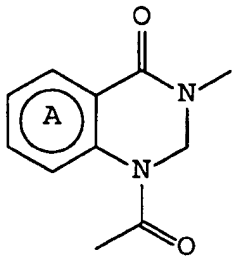
(b)



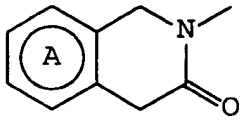
(c)



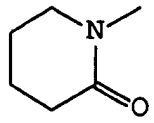
(d)



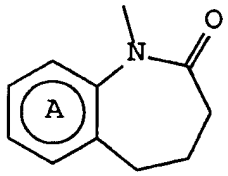
(e)



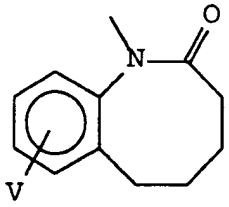
(g)



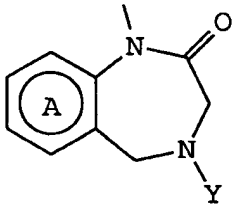
(h)



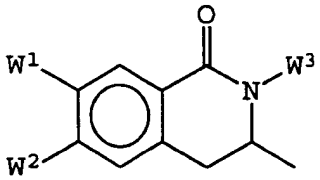
(j)



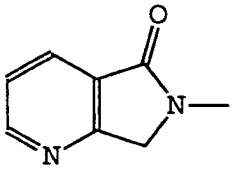
(k)



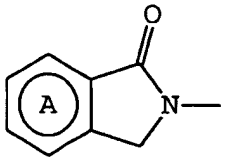
(l)



(n)



(p)



(q)

wherein

Y in the formula (l) is a hydrogen atom or a C_{1-6} alkyl group; V in the formula (k) is a hydrogen atom or a C_{1-6} alkoxy group; W^1 and W^2 in the formula (n) are each a hydrogen atom, a C_{1-6} alkyl or a C_{1-6} alkoxy group; W^3

in formula (n) is a hydrogen atom or a C_{1-6} alkyl group; and the phenyl group A in the formulae (a)-(g), (j) , (l) and (q) may optionally be substituted by a C_{1-6} alkyl group or a C_{1-6} alkoxy group;

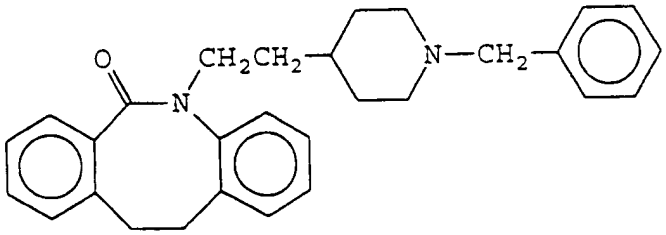
K is a phenylalkyl group wherein the phenyl may optionally be substituted by a C_{1-6} alkyl group which may optionally be halogenated, a C_{1-6} alkoxy group, a nitro group, a halogen atom, a carboxyl group, a benzyloxy group, a C_{1-6} alkoxycarbonyl group, an amino group, a C_{1-6} monoalkylamino group, a C_{1-6} dialkylamino group, a carbamoyl group, a C_{1-6} acylamino group, a cyclohexyloxycarbonyl group, a C_{1-6} alkylaminocarbonyl group, a C_{1-6} alkylcarbonyloxy group, a hydroxyl group, a formyl group or a C_{1-6} alkoxy-C_{1-6} alkyl group; and

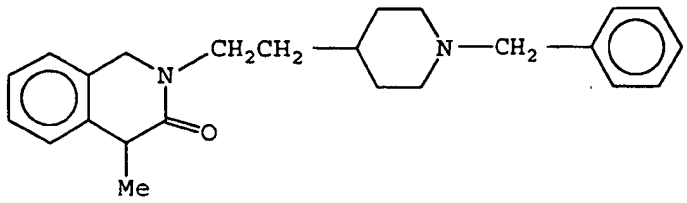
r is an integer of from 0 to 6,

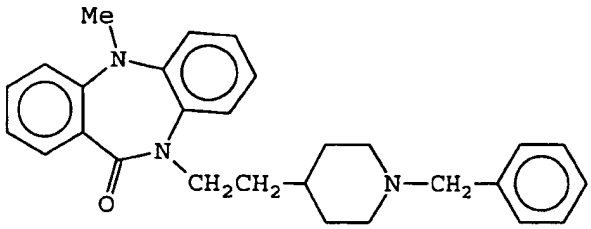
with the proviso that if r is 0, then J is neither the group (a) nor the group (q), and with the proviso that if K is a benzyl group and r is 0, then J is not the group (d).

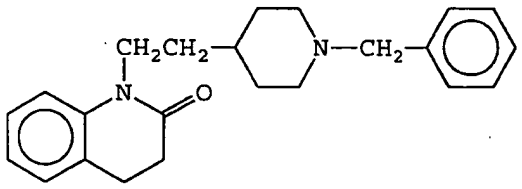
2. A cyclic amine compound or pharmaceutically acceptable salt thereof according to Claim 1, wherein r is 2.

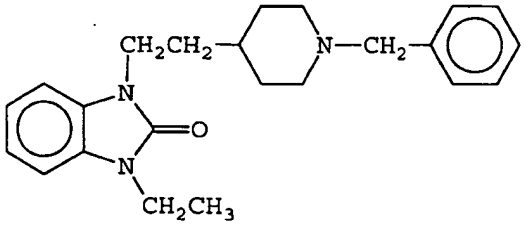
3. A cyclic amine of any one of the formulae:

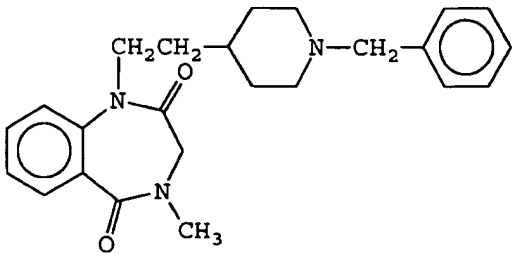




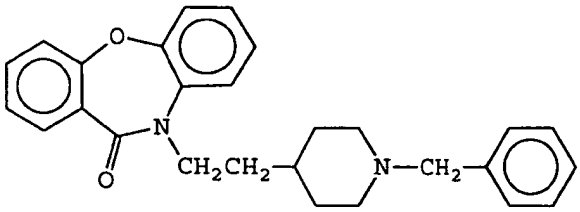








or;



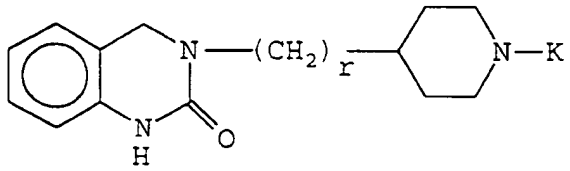
4. A pharmaceutical composition which comprises a pharmacologically effective amount of a cyclic amine compound according to any preceding Claim, or a pharmacologically acceptable salt thereof, and a pharmacologically accept-

able carrier.

5. The use of:

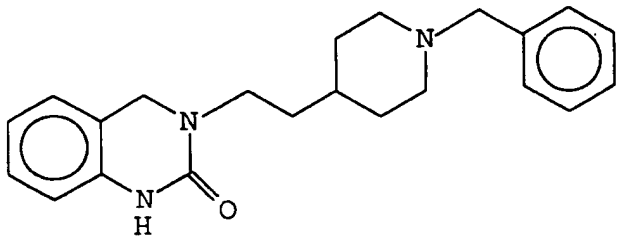
(a') a cyclic amine compound according to any preceding Claim;
(b') a compound of general formula (XXV) of Claim 1 in which r is 0 and J is either the group (a) or the group (q);
(c') a compound of general formula (XXV) of Claim 1 in which K is benzyl, r is 0 and J is the group (d); or
(d') a pharmacologically acceptable salt of any of (a'), (b') or (c') above;
for preparing a medicament for the treatment of a disease caused by acetylcholinesterase activity.

6. The use of a cyclic amine compound of the general formula



wherein the phenyl group of the quinazolinone moiety may optionally be substituted by a C_{1-6} alkyl group or a C_{1-6} alkoxy group, and K and r are as defined in Claim 1 or a pharmacologically acceptable salt thereof, for preparing a medicament for the treatment of a disease caused by acetylcholinesterase activity.

7. The use according to Claim 6, wherein the cyclic amine compound has the formula:

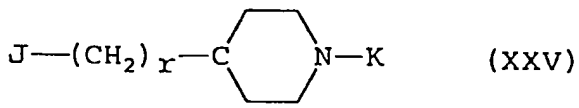


8. The use as claimed in any of Claims 5-7, wherein the medicament is effective against senile dementia.

9. The use as claimed in Claim 8, wherein the medicament is effective against senile dementia of the Alzheimer type.

Claims for the following Contracting States : ES, GR

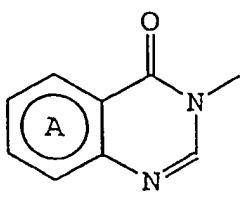
1. A process for preparing a pharmaceutical composition effective against a disease due to acetylcholinesterase activity comprising the step of mixing a pharmaceutically acceptable carrier and a cyclic amine compound having the following formula (XXV) or a pharmacologically acceptable salt thereof:



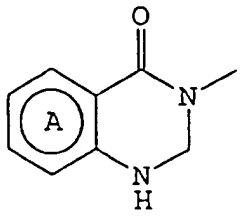
(XXV)

wherein

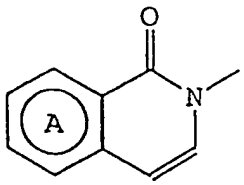
J is a monovalent group selected from



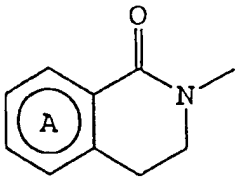
(a)



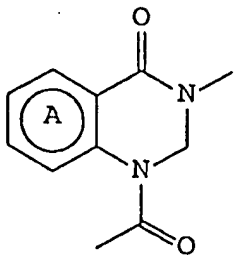
(b)



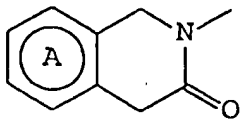
(c)



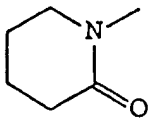
(d)



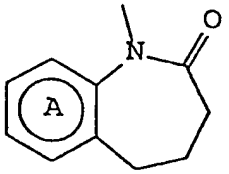
(e)



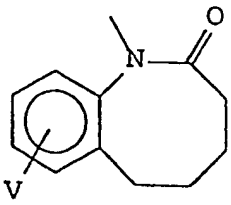
(g)



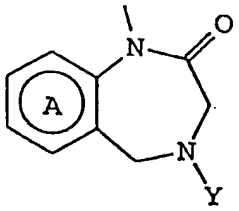
(h)



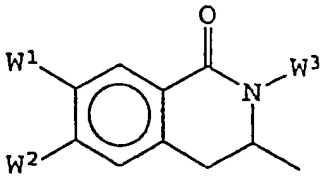
(j)



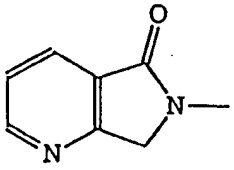
(k)



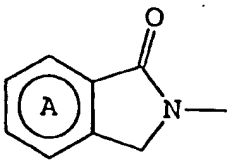
(l)



(n)



(p)



(q)

wherein

Y in the formula (l) is a hydrogen atom or a C_{1-6} alkyl group; V in the formula (k) is a hydrogen atom or a C_{1-6} alkoxy group; W^1 and W^2 in the formula (n) are each a hydrogen atom, a C_{1-6} alkyl or a C_{1-6} alkoxy group; W^3

in formula (n) is a hydrogen atom or a C_{1-6} alkyl group; and the phenyl group A in the formulae (a)-(g), (j), (l) and (q) may optionally be substituted by a C_{1-6} alkyl group or a C_{1-6} alkoxy group;

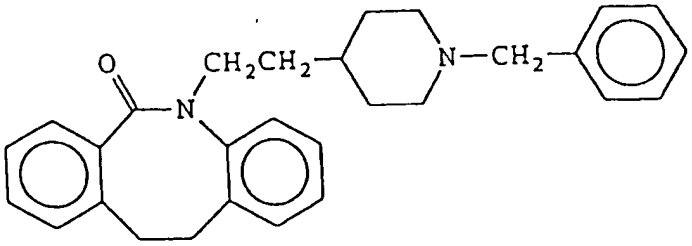
K is a phenylalkyl group wherein the phenyl may optionally be substituted by a C_{1-6} alkyl group which may optionally be halogenated, a C_{1-6} alkoxy group, a nitro group, a halogen atom, a carboxyl group, a benzyloxy group, a C_{1-6} alkoxycarbonyl group, an amino group, a C_{1-6} monoalkylamino group, a C_{1-6} dialkylamino group, a carbamoyl group, a C_{1-6} acylamino group, a cyclohexyloxycarbonyl group, a C_{1-6} alkylaminocarbonyl group, a C_{1-6} alkylcarbonyloxy group, a hydroxyl group, a formyl group or a C_{1-6} alkoxy-C_{1-6} alkyl group; and

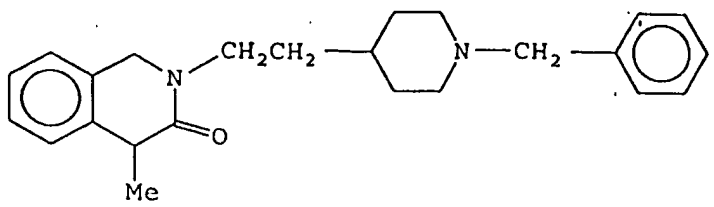
r is an integer of from 0 to 6,

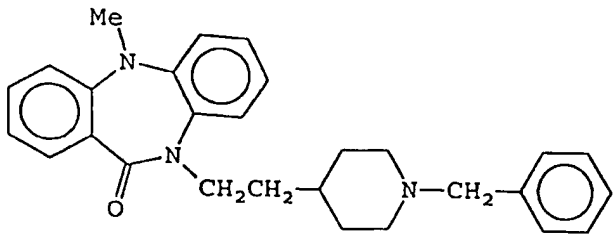
with the proviso that if r is 0, then J is neither the group (a) nor the group (q), and with the proviso that if K is a benzyl group and r is 0, then J is not the group (d).

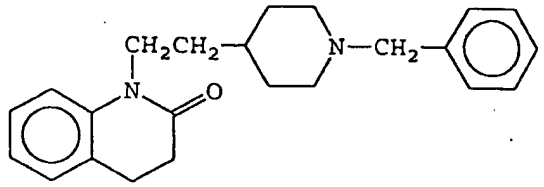
2. A process according to Claim 1, wherein r in formula (XXV) is 2.

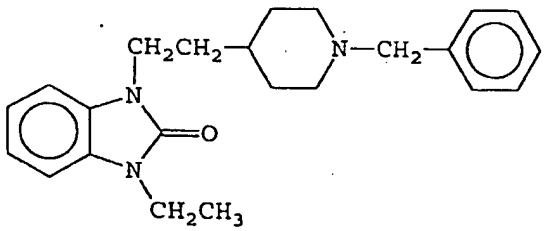
3. A process for preparing a pharmaceutical composition effective against a disease due to acetylcholinesterase activity comprising the step of mixing a pharmaceutically acceptable carrier and a cyclic amine of any one of the formulae:

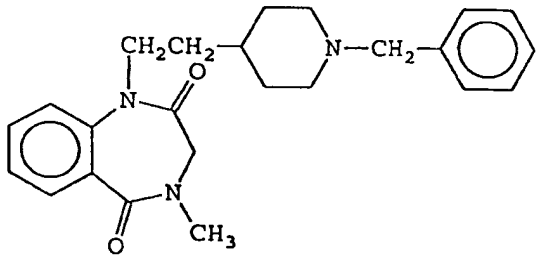




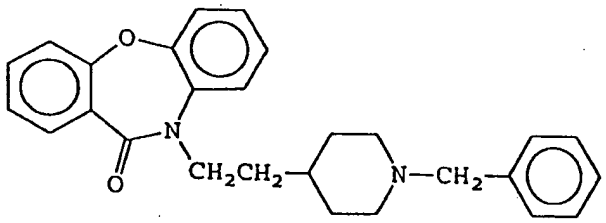








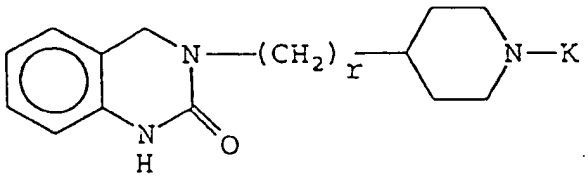
or;



4. The use of:

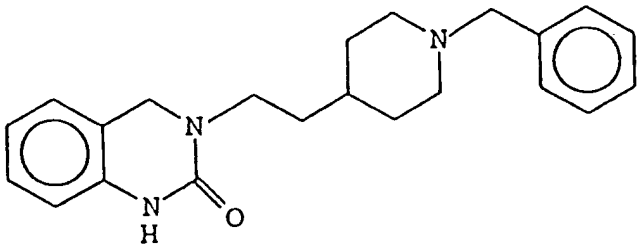
(a') a cyclic amine compound according to any preceding Claim;
(b') a compound of general formula (XXV) of Claim 1 in which r is 0 and J is either the group (a) or the group (q);
(c') a compound of general formula (XXV) of Claim 1 in which K is benzyl, r is 0 and J is the group (d); or
(d') a pharmacologically acceptable salt of any of (a'), (b') or (c') above;
for preparing a medicament for the treatment of a disease caused by acetylcholinesterase activity.

5. The use of a cyclic amine compound of the general formula



wherein the phenyl group of the quinazolinone moiety may optionally be substituted by a C_{1-6} alkyl group or a C_{1-6} alkoxy group, and K and r are as defined in Claim 1 or a pharmacologically acceptable salt thereof, for preparing a medicament for the treatment of a disease caused by acetylcholinesterase activity.

6. The use according to Claim 5, wherein the cyclic amine compound has the formula:



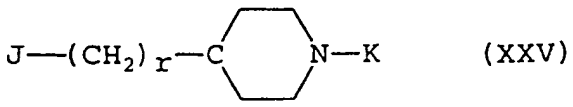
7. The use as claimed in any of Claims 4-6, wherein the medicament is effective against senile dementia.

8. The use as claimed in Claim 7, wherein the medicament is effective against senile dementia of the Alzheimer type.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, LI, DE, FR, GB, IT, LU, NL, SE

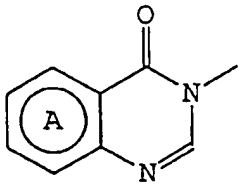
1. Cyclische Amin-Verbindung mit der folgenden Formel (XXV) oder pharmakologisch annehmbares Salz hiervon:



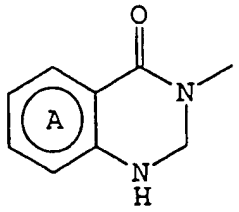
(XXV)

wobei

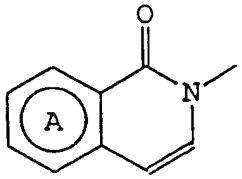
J eine monovalente Gruppe ist, ausgewählt aus:



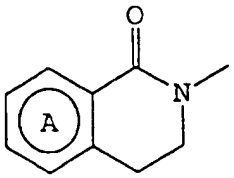
(a)



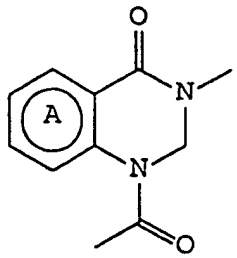
(b)



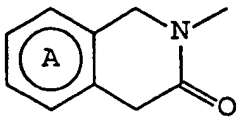
(c)



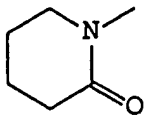
(d)



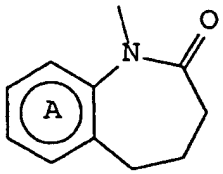
(e)



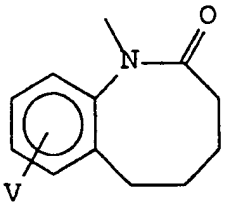
(g)



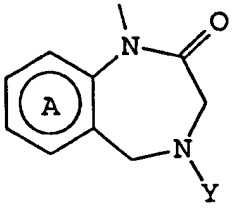
(h)



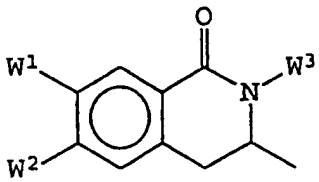
(j)



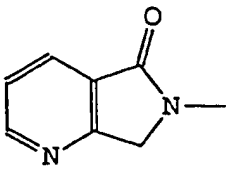
(k)



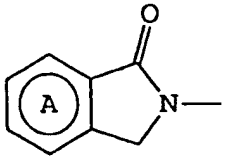
(l)



(n)



(p)



(q)

wobei

Y in der Formel (l) ein Wasserstoffatom oder eine C_{1-6}-Alkyl-Gruppe ist; V in der Formel (k) ein Wasserstoff-

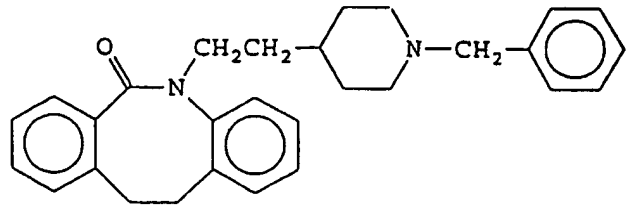
atom oder eine C_{1-6}-Alkoxy-Gruppe ist; W^1 und W^2 in der Formel (n) jeweils ein Wasserstoffatom, eine C_{1-6}-Alkyl-Gruppe oder eine C_{1-6}-Alkoxy-Gruppe sind; W^3 in der Formel (n) ein Wasserstoffatom oder eine C_{1-6}-Alkyl-Gruppe ist; und die Phenyl-Gruppe A in den Formeln (a)-(g), (j), (l) und (q) wahlweise durch eine C_{1-6}-Alkyl-Gruppe oder eine C_{1-6}-Alkoxy-Gruppe substituiert sein kann;

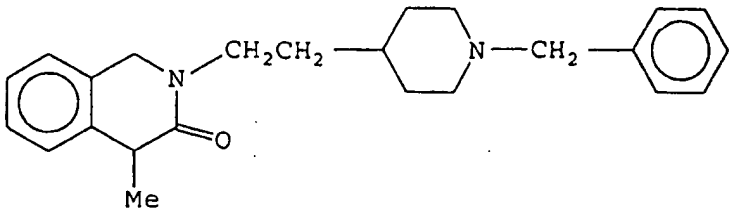
K eine Phenylalkyl-Gruppe ist, in der die Phenyl-Gruppe wahlweise durch eine C_{1-6}-Alkyl-Gruppe, die wahlweise halogeniert sein kann, eine C_{1-6}-Alkoxy-Gruppe, eine Nitro-Gruppe, ein Halogenatom, eine Carboxy-Gruppe, eine Benzyloxy-Gruppe, eine C_{1-6}-Alkoxycarbonyl-Gruppe, eine Amino-Gruppe, eine C_{1-6}-Monoalkylamino-Gruppe, eine C_{1-6}-Dialkylamino-Gruppe, eine Carbamoyl-Gruppe, eine C_{1-6}-Acylamino-Gruppe, eine Cyclohexyloxycarbonyl-Gruppe, eine C_{1-6}-Alkylaminocarbonyl-Gruppe, eine C_{1-6}-Alkylcarbonyloxy-Gruppe, eine Hydroxyl-Gruppe, eine Formyl-Gruppe oder eine C_{1-6}-Alkoxy-C_{1-6}-alkyl-Gruppe substituiert sein kann; und

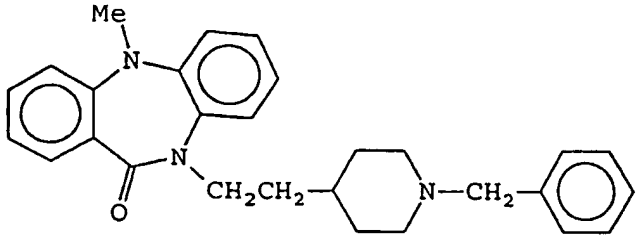
r eine ganze Zahl von 0 bis 6 ist,
unter der Voraussetzung, daß, wenn r 0 ist, J weder die Gruppe (a) noch die Gruppe (q) ist, und unter der Voraussetzung, daß, wenn K eine Benzyl-Gruppe ist und r 0 ist, J nicht die Gruppe (d) ist.

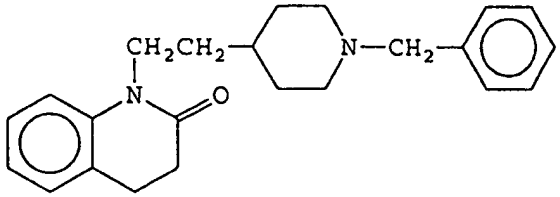
2. Cyclische Amin-Verbindung oder pharmazeutisch annehmbares Salz hiervon gemäß Anspruch 1, wobei r 2 ist.

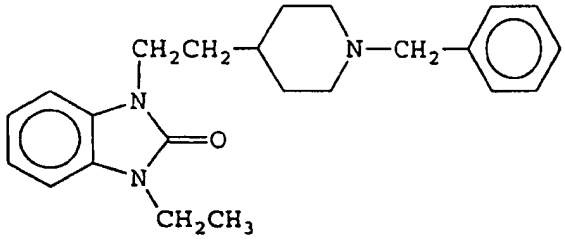
3. Cyclische Amin-Verbindung eine der Formeln:

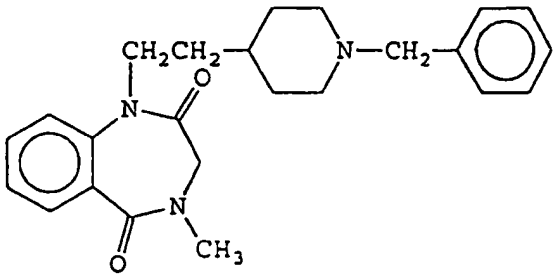




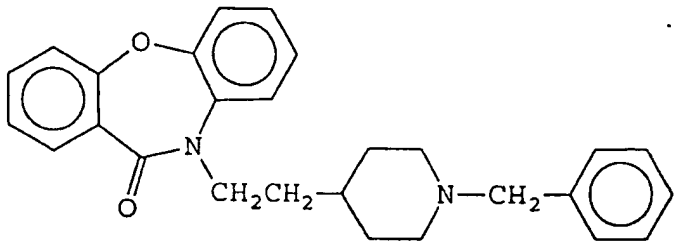








oder



4. Pharmazeutische Zusammensetzung, die eine pharmakologisch wirksame Menge einer cyclischen Amin-Verbindung gemäß einem der vorhergehenden Ansprüche oder ein pharmakologisch annehmbares Salz hiervon und einen pharmakologisch annehmbaren Träger umfaßt.

5. Verwendung:

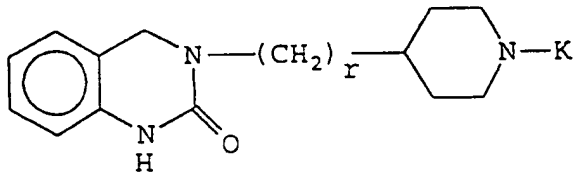
(a') einer cyclischen Amin-Verbindung gemäß einem der vorhergehenden Ansprüche;

(b') einer Verbindung der allgemeinen Formel (XXV) von Anspruch 1, in der r gleich 0 ist und J entweder die Gruppe (a) oder die Gruppe (g) ist;

(c') einer Verbindung der allgemeinen Formel (XXV) von Anspruch 1, in der K Benzyl ist, r 0 ist und J die Gruppe (d) ist; oder

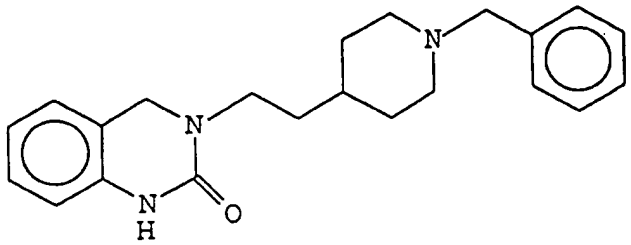
(d') eines pharmakologisch annehmbaren Salzes von einem von (a'), (b') oder (c');
zur Herstellung eines Medikamentes zur Behandlung einer Krankheit, die durch Acetylcholinesterase-Aktivität bewirkt wird.

6. Verwendung einer cyclischen Amin-Verbindung der allgemeinen Formel:



wobei die Phenyl-Gruppe des Chinazolinon-Teils wahlweise durch eine C_{1-6}-Alkyl-Gruppe oder eine C_{1-6}-Alkoxy-Gruppe substituiert sein kann, und K und r die gleiche Bedeutung wie in Anspruch 1 haben, oder eines pharmakologisch annehmbaren Salzes hiervon, zur Herstellung eines Medikamentes zur Behandlung einer Krankheit, die durch Acetylcholinesterase-Aktivität bewirkt wird.

7. Verwendung gemäß Anspruch 6, wobei die cyclische Amin-Verbindung die Formel hat:

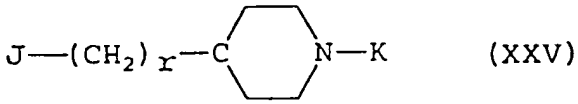


8. Verwendung gemäß einem der Ansprüche 5 bis 7, wobei das Medikament gegen senile Dementia wirksam ist.

9. Verwendung gemäß Anspruch 8, wobei das Medikament gegen Alzheimersche senile Dementia wirksam ist.

Patentansprüche für folgende Vertragsstaaten : ES, GR

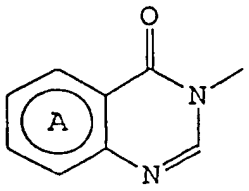
1. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, die gegen eine durch Acetylcholinesterase-Aktivität bedingte Krankheit wirksam ist, umfassend den Schritt des Mischens eines pharmazeutisch annehmbaren Trägers und einer cyclischen Amin-Verbindung mit der folgenden Formel (XXV) oder eines pharmakologisch annehmbaren Salzes hiervon:



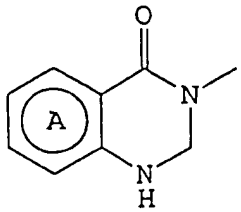
(XXV)

wobei

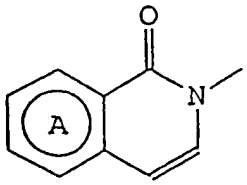
J eine monovalente Gruppe ist, ausgewählt aus:



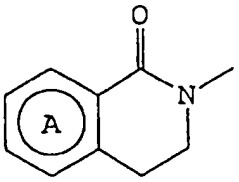
(a)



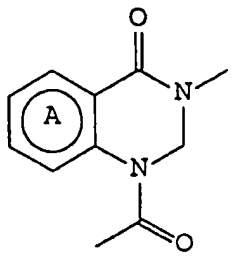
(b)



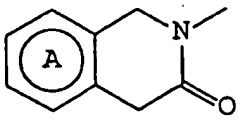
(c)



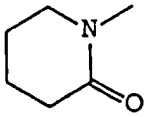
(d)



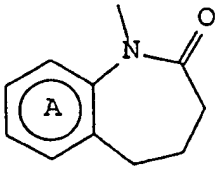
(e)



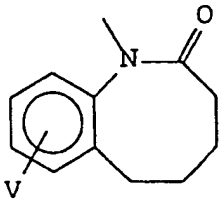
(g)



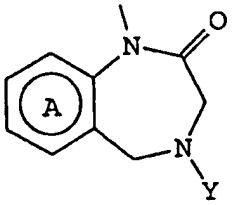
(h)



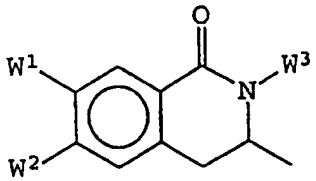
(j)



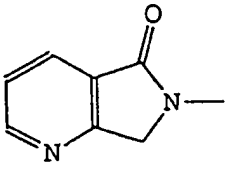
(k)



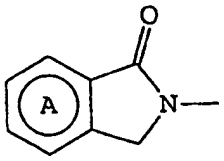
(l)



(n)



(p)



(q)

wobei

Y in der Formel (l) ein Wasserstoffatom oder eine C_{1-6}-Alkyl-Gruppe ist; V in der Formel (k) ein Wasserstoff-

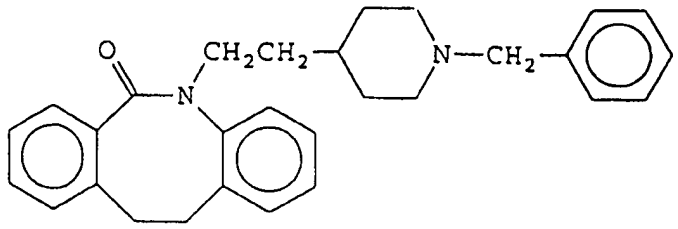
atom oder eine C_{1-6}-Alkoxy-Gruppe ist; W^1 und W^2 in der Formel (n) jeweils ein Wasserstoffatom, eine C_{1-6}-Alkyl-Gruppe oder eine C_{1-6}-Alkoxy-Gruppe sind; W^3 in der Formel (n) ein Wasserstoffatom oder eine C_{1-6}-Alkyl-Gruppe ist; und die Phenyl-Gruppe A in den Formeln (a)-(g), (j), (l) und (g) wahlweise durch eine C_{1-6}-Alkyl-Gruppe oder eine C_{1-6}-Alkoxy-Gruppe substituiert sein kann;

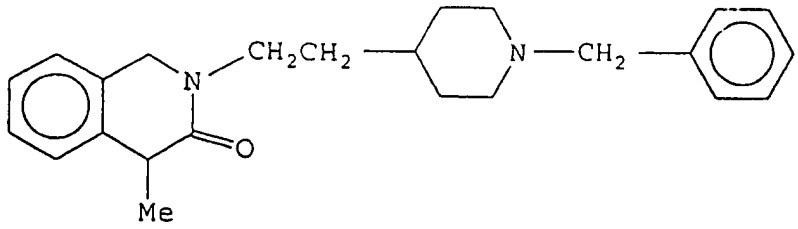
K eine Phenylalkyl-Gruppe ist, in der die Phenyl-Gruppe wahlweise durch eine C_{1-6}-Alkyl-Gruppe, die wahlweise halogeniert sein kann, eine C_{1-6}-Alkoxy-Gruppe, eine Nitro-Gruppe, ein Halogenatom, eine Carboxy-Gruppe, eine Benzyloxy-Gruppe, eine C_{1-6}-Alkoxycarbonyl-Gruppe, eine Amino-Gruppe, eine C_{1-6}-Monoalkylamino-Gruppe, eine C_{1-6}-Dialkylamino-Gruppe, eine Carbamoyl-Gruppe, eine C_{1-6}-Acylamino-Gruppe, eine Cyclohexyloxycarbonyl-Gruppe, eine C_{1-6}-Alkylaminocarbonyl-Gruppe, eine C_{1-6}-Alkylcarbonyloxy-Gruppe, eine Hydroxyl-Gruppe, eine Formyl-Gruppe oder eine C_{1-6}-Alkoxy-C_{1-6}-alkyl-Gruppe substituiert sein kann; und

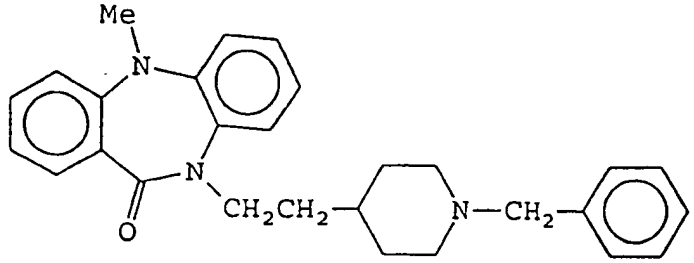
r eine ganze Zahl von 0 bis 6 ist,
unter der Voraussetzung, daß, wenn r 0 ist, J weder die Gruppe (a) noch die Gruppe (q) ist, und unter der Voraussetzung, daß, wenn K eine Benzyl-Gruppe ist und r 0 ist, J nicht die Gruppe (d) ist.

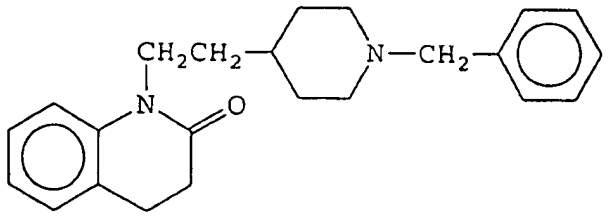
2. Verfahren gemäß Anspruch Anspruch 1, wobei r in der Formel (XXV) 2 ist.

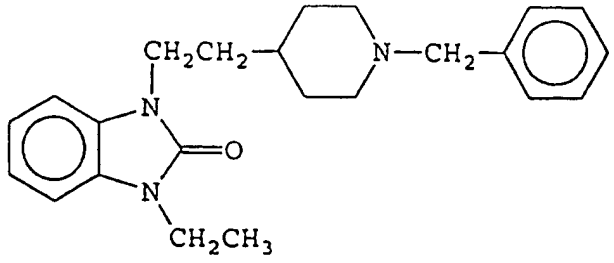
3. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, die gegen eine durch Acetylcholinesterase-Aktivität bedingte Krankheit wirksam ist, umfassend den Schritt des Mischens eines pharmazeutisch annehmbaren Trägers und einer cyclischen Amin-Verbindung einer der Formeln:

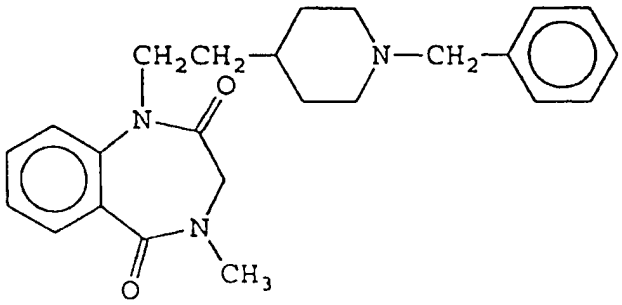




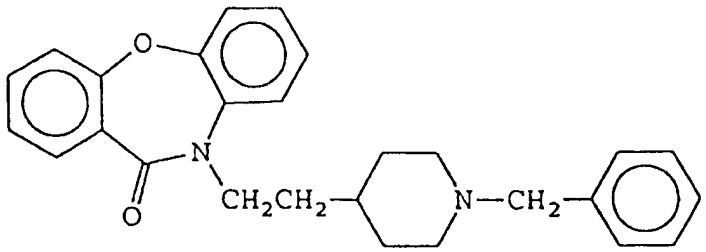








oder



4. Verwendung:

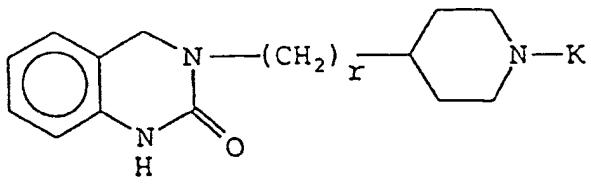
(a') einer cyclischen Amin-Verbindung gemäß einem der vorhergehenden Ansprüche;

(b') einer Verbindung der allgemeinen Formel (XXV) von Anspruch 1, in der r gleich 0 ist und J entweder die Gruppe (a) oder die Gruppe (q) ist;

(c') einer Verbindung der allgemeinen Formel (XXV) von Anspruch 1, in der K Benzyl ist, r 0 ist und J die Gruppe (d) ist; oder

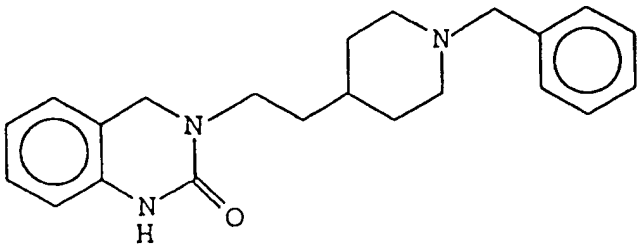
(d') eines pharmakologisch annehmbaren Salzes von einem von (a'), (b') oder (c');
zur Herstellung eines Medikamentes zur Behandlung einer Krankheit, die durch Acetylcholinesterase-Aktivität bewirkt wird.

5. Verwendung einer cyclischen Amin-Verbindung der allgemeinen Formel:



wobei die Phenyl-Gruppe des Chinazolinon-Teils wahlweise durch eine C_{1-6}-Alkyl-Gruppe oder eine C_{1-6}-Alkoxy-Gruppe substituiert sein kann, und K und r die gleiche Bedeutung wie in Anspruch 1 haben, oder eines pharmakologisch annehmbaren Salzes hiervon, zur Herstellung eines Medikamentes zur Behandlung einer Krankheit, die durch Acetylcholinesterase-Aktivität bewirkt wird.

6. Verwendung gemäß Anspruch 5, wobei die cyclische Amin-Verbindung die Formel hat:



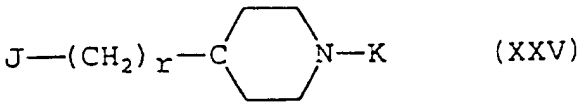
7. Verwendung gemäß einem der Ansprüche 4 bis 6, wobei das Medikament gegen senile Dementia wirksam ist.

8. Verwendung gemäß Anspruch 7, wobei das Medikament gegen Alzheimersche senile Dementia wirksam ist.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, LI, DE, FR, GB, IT, LU, NL, SE

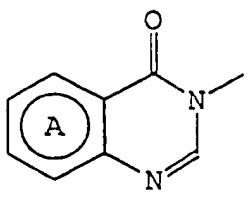
1. Composé d'amine cyclique ayant la formule (XXV) suivante, ou sel pharmacologiquement acceptable de celui-ci :



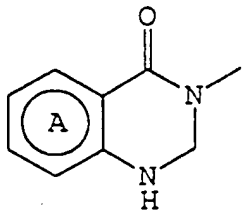
(XXV)

où

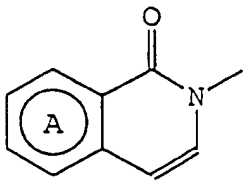
J est un groupe monovalent choisi parmi



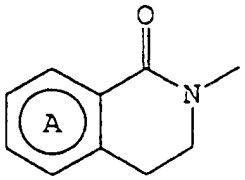
(a)



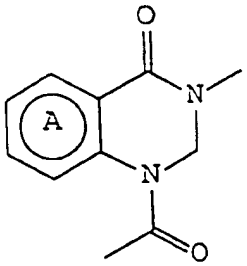
(b)



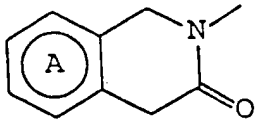
(c)



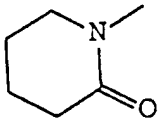
(d)



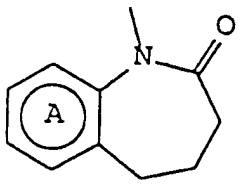
(e)



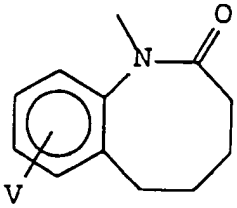
(g)



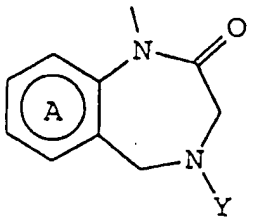
(h)



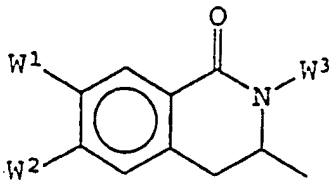
(j)



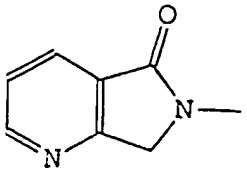
(k)



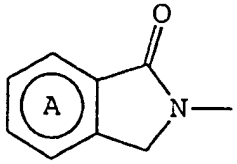
(l)



(n)



(p)



(q)

où

Y, dans la formule (l), est un atome d'hydrogène ou un groupe alkyle en C_1-C_6 ; V, dans la formule (k), est un atome d'hydrogène ou un groupe alcoxy en C_1-C_6 ; W^1 et W^2, dans la formule (n), sont chacun un atome d'hydrogène, un groupe alkyle en C_1-C_6 ou un groupe alcoxy en C_1-C_6 ; W^3, dans la formule (n), est un atome d'hydrogène ou un groupe alkyle en C_1-C_6 ; et le groupe phényle A, dans les formules (a) à (g), (j), (l) et (q) peut facultativement être substitué par un groupe alkyle en C_1-C_6 ou un groupe alcoxy en C_1-C_6 ;

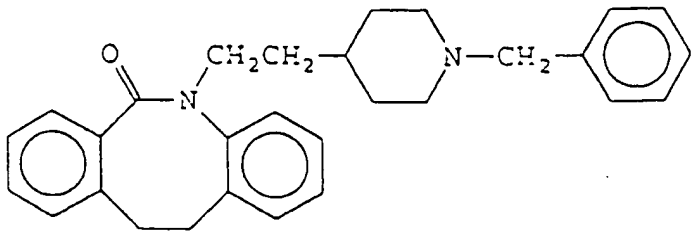
K est un groupe phénylalkyle dont le groupe phényle peut facultativement être substitué par un groupe alkyle en C_1-C_6 qui peut facultativement être halogéné, un groupe alcoxy en C_1-C_6, un groupe nitro, un atome d'halogène, un groupe carboxyle, un groupe benzyloxy, un groupe (alcoxy en C_1-C_6)carbonyle, un groupe amino, un groupe monoalkylamino en C_1-C_6, un groupe di(alkyl en C_1-C_6)amino, un groupe carbamoyle, un groupe acylamino en C_1-C_6, un groupe cyclohexyloxycarbonyle, un groupe (alkyl en C_1-C_6)aminocarbonyle, un groupe (alkyle en C_1-C_6)carbonyloxy, un groupe hydroxyle, un groupe formyle ou un groupe (alcoxy en C_1-C_6)-alkyle en C_1-C_6 ; et

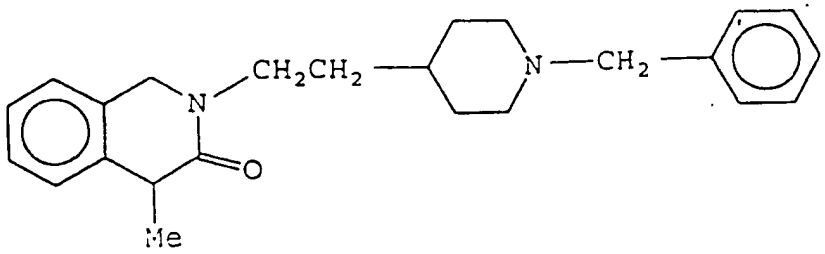
r est un nombre entier de 0 à 6,

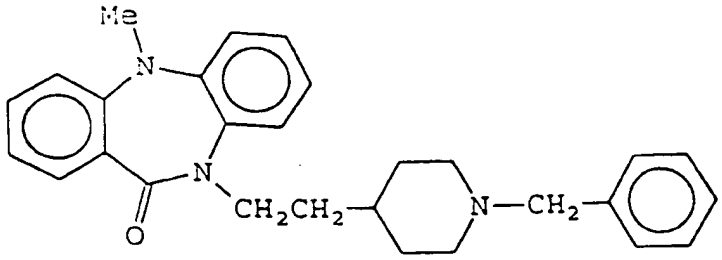
avec la condition que si r est 0, alors J ne soit ni le groupe (a) ni le groupe (q), et avec la condition que si K est un groupe benzyle et r est 0, alors J ne soit pas le groupe (d).

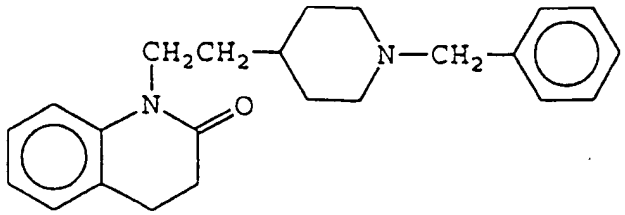
2. Composé d'amine cyclique ou sel pharmaceutiquement acceptable de celui-ci selon la revendication 1, dans lequel r est 2.

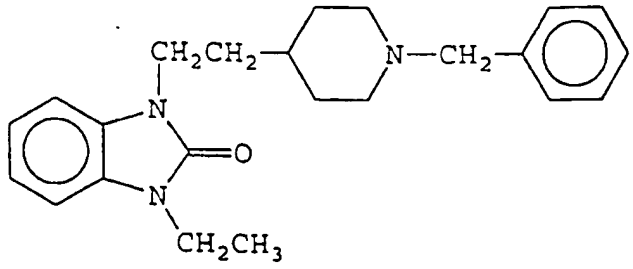
3. Amine cyclique de l'une quelconque des formules :

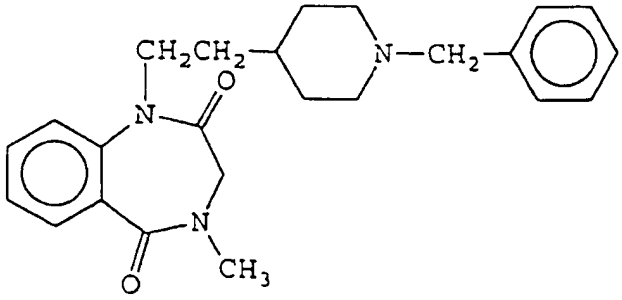




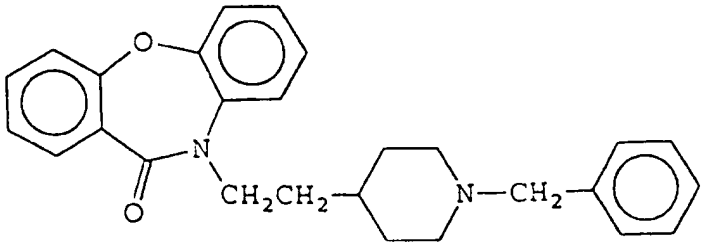








ou

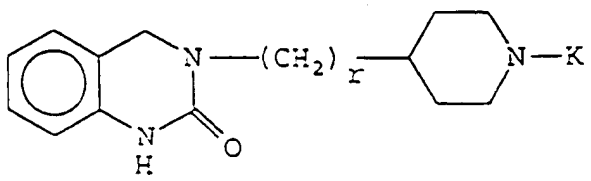


4. Composition pharmaceutique qui comprend une quantité pharmacologiquement efficace d'un composé d'amine cyclique selon l'une quelconque des revendications précédentes, ou d'un sel pharmacologiquement acceptable de celui-ci, et un véhicule pharmacologiquement acceptable.

5. Utilisation de :

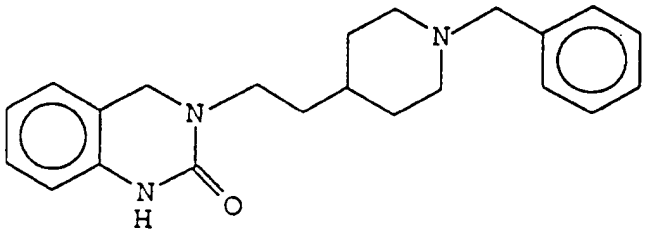
(a') un composé d'amine cyclique selon l'une quelconque des revendications précédentes ;
(b') un composé de formule générale (XXV) de la revendication 1, dans lequel r est 0 et J est soit le groupe (a), soit le groupe (q) ;
(c') un composé de formule générale (XXV) de la revendication 1, dans lequel K est le groupe benzyle, r est 0 et J est le groupe (d) ; ou
(d') un sel pharmacologiquement acceptable de l'un quelconque de (a'), (b') ou (c') ci-dessus ; pour préparer un médicament destiné au traitement d'une maladie provoquée par l'activité acétylcholinestérase

6. Utilisation d'un composé d'amine cyclique de formule générale



où le groupe phényle du fragment quinazolinone peut facultativement être substitué par un groupe alkyle en C_1-C_6 ou un groupe alcoxy en C_1-C_6, et K et r sont tels que définis dans la revendication 1, ou d'un sel pharmacologiquement acceptable de celui-ci, pour préparer un médicament destiné au traitement d'une maladie provoquée par l'activité acétylcholinestérase.

7. Utilisation selon la revendication 6, dans laquelle le composé d'amine cyclique répond à la formule :

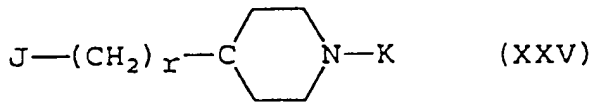


8. Utilisation telle que revendiquée dans l'une quelconque des revendications 5 à 7, dans laquelle le médicament est efficace contre la démence sénile.

9. Utilisation telle que revendiquée dans la revendication 8, dans laquelle le médicament est efficace contre la démence sénile du type d'Alzheimer.

Revendications pour les Etats contractants suivants : ES, GR

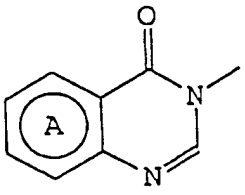
1. Procédé pour préparer une composition pharmaceutique efficace contre une maladie due à l'activité acétylcholinestérase, comprenant l'étape consistant à mélanger un véhicule pharmaceutiquement acceptable et un composé d'amine cyclique ayant la formule (XXV) suivante ou un sel pharmacologiquement acceptable de celui-ci :



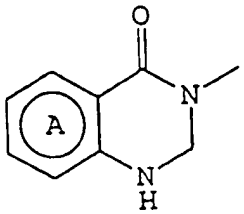
(XXV)

où

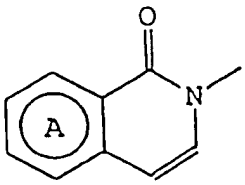
J est un groupe monovalent choisi parmi



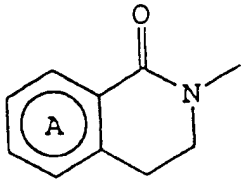
(a)



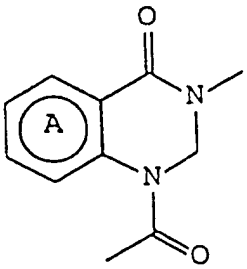
(b)



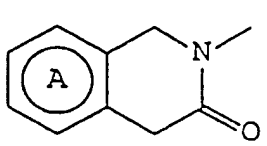
(c)



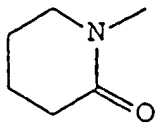
(d)



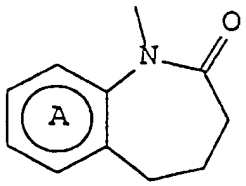
(e)



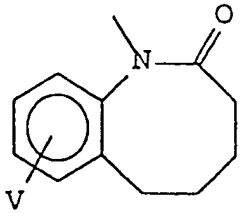
(g)



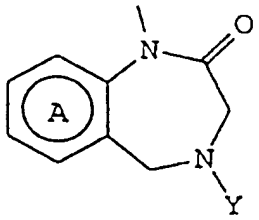
(h)



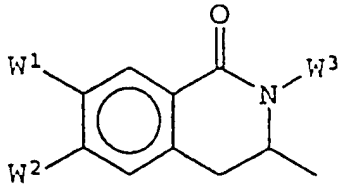
(j)



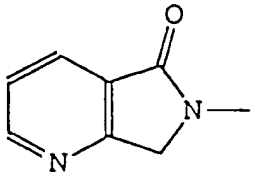
(k)



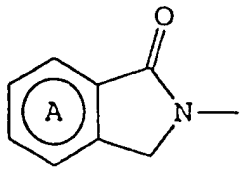
(l)



(n)



(p)



(q)

où

Y, dans la formule (l), est un atome d'hydrogène ou un groupe alkyle en C_1-C_6 ; V, dans la formule (k), est un atome d'hydrogène ou un groupe alcoxy en C_1-C_6 ; W^1 et W^2, dans la formule (n), sont chacun un atome d'hydrogène, un groupe alkyle en C_1-C_6 ou un groupe alcoxy en C_1-C_6 ; W^3, dans la formule (n), est un atome d'hydrogène ou un groupe alkyle en C_1-C_6 ; et le groupe phényle A, dans les formules (a) à (g), (j), (l) et (q) peut facultativement être substitué par un groupe alkyle en C_1-C_6 ou un groupe alcoxy en C_1-C_6 ;

K est un groupe phénylalkyle dont le groupe phényle peut facultativement être substitué par un groupe alkyle en C_1-C_6 qui peut facultativement être halogéné, un groupe alcoxy en C_1-C_6, un groupe nitro, un atome d'halogène, un groupe carboxyle, un groupe benzyloxy, un groupe (alcoxy en C_1-C_6)carbonyle, un groupe amino, un groupe monoalkylamino en C_1-C_6, un groupe di(alkyle en C_1-C_6)amino, un groupe carbamoyle, un groupe acylamino en C_1-C_6, un groupe cyclohexyloxycarbonyle, un groupe (alkyle en C_1-C_6)aminocarbonyle, un groupe (alkyle en C_1-C_6)carbonyloxy, un groupe hydroxyle, un groupe formyle ou un groupe (alcoxy en C_1-C_6)alkyle en C_1-C_6 ; et

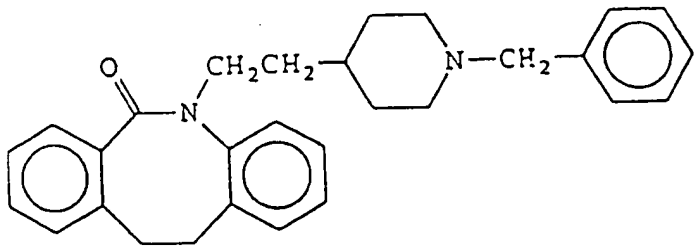
r est un nombre entier de 0 à 6,

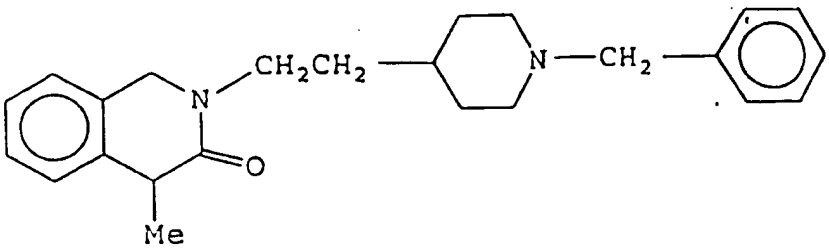
avec la condition que si r est 0, alors J ne soit ni le groupe (a) ni le groupe (q), et avec la condition que

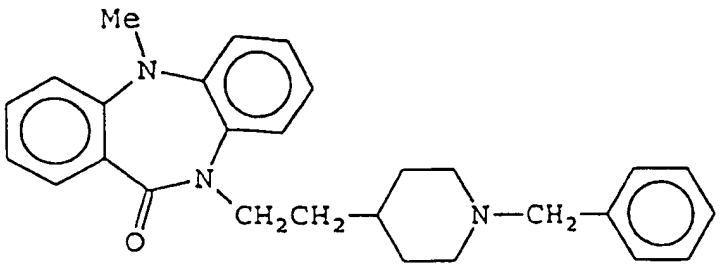
si K est un groupe benzyle et r est 0, alors J ne soit pas le groupe (d).

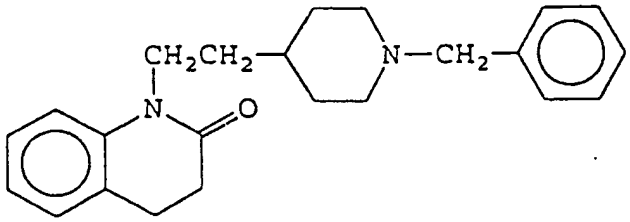
2. Procédé selon la revendication 1, dans lequel r, dans la formule (XXV), est 2.

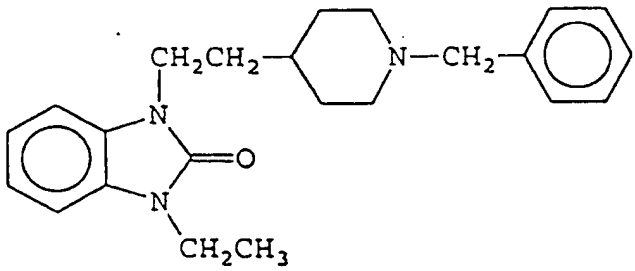
3. Procédé pour préparer une composition pharmaceutique efficace contre une maladie due à l'activité acétylcholinestérase, comprenant l'étape consistant à mélanger un véhicule pharmaceutiquement acceptable et une amine cyclique de l'une quelconque des formules :

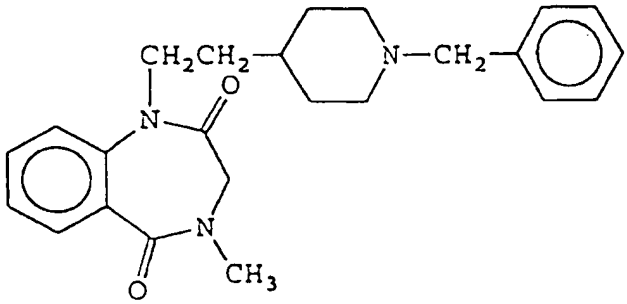




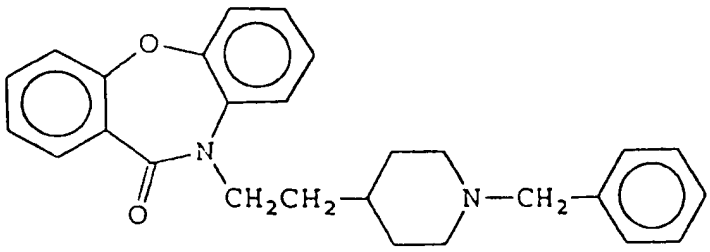








ou



4. Utilisation de :

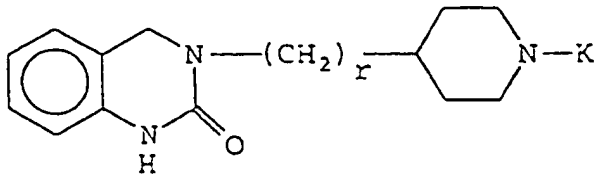
(a') un composé d'amine cyclique selon l'une quelconque des revendications précédentes ;

(b') un composé de formule générale (XXV) de la revendication 1, dans lequel r est 0 et J est soit le groupe (a), soit le groupe (q) ;

(c') un composé de formule générale (XXV) de la revendication 1, dans lequel K est le groupe benzyle, r est 0 et J est le groupe (d) ; ou

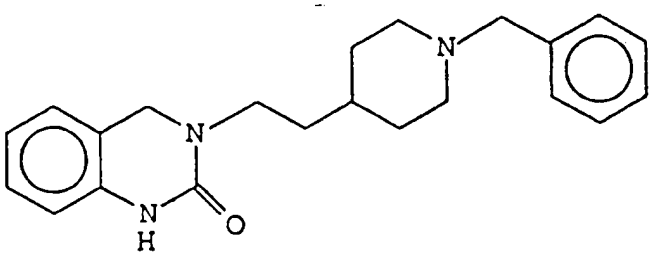
(d') un sel pharmacologiquement acceptable de l'un quelconque de (a'), (b') ou (c') ci-dessus ; pour préparer un médicament destiné au traitement d'une maladie provoquée par l'activité acétylcholinestérase.

5. Utilisation d un composé d'amine cyclique de formule générale



où le groupe phényle du fragment quinazolinone peut facultativement être substitué par un groupe alkyle en C_1-C_6 ou un groupe alcoxy en C_1-C_6, et K et r sont tels que définis dans la revendication 1, ou d'un sel pharmacologiquement acceptable de celui-ci, pour préparer un médicament destiné au traitement d'une maladie provoquée par l'activité acétylcholinestérase.

6. Utilisation selon la revendication 5, dans laquelle le composé d'amine cyclique répond à la formule :



7. Utilisation telle que revendiquée dans l'une quelconque des revendications 4 à 6, dans laquelle le médicament est efficace contre la démence sénile.

8. Utilisation telle que revendiquée dans la revendication 7, dans laquelle le médicament est efficace contre la démence sénile du type d'Alzheimer.